Allergic Diseases

CURRENT ◊ CLINICAL ◊ PRACTICE

Allergic Diseases: *Diagnosis and Treatment,*
edited by *PHIL LIEBERMAN AND JOHN A. ANDERSON,* 1997
Osteoporosis: *Diagnostic and Therapeutic Principles,*
edited by *CLIFFORD J. ROSEN,* 1996

Allergic Diseases

Diagnosis and Treatment

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SPRINGER SCIENCE+BUSINESS MEDIA, LLC

Originally published by Humana Press Inc. in 1997
Softcover reprint of the hardcover 1st edition 1997

Cover design by Patricia F. Cleary

This publication is printed on acid-free paper.
ANSI Z39.48-1984 (American National Standards Institute) Permanence of Paper for Printed Library Materials).

Library of Congress Cataloging-in-Publication Data

Allergic diseases: diagnosis and treatment/edited by Phil Lieberman and John A. Anderson
p. cm.—(Current clinical practice)
Includes index.
ISBN 978-1-4757-2593-3 ISBN 978-1-4757-2591-9 (eBook)
DOI 10.1007/978-1-4757-2591-9
1. Allergy. I. Lieberman, Phil L. II. Anderson, John A. (John Albert), 1935–. III. Series.
[DNLM: 1. Hypersensitivity—diagnosis. 2. Hypersensitivity—therapy. WD 300 A43108 1997]
RC584.A343 1997
616.97—dc20
DNLM/DLC
for Library of Congress 96-38857
CIP

PREFACE

We have experienced, in our over 60 years of combined teaching and practice of allergy and immunology, most of the challenges that our field can present. We felt it desirable to share this experience with other physicians engaged in the care of the allergic patient. In order to do that we assembled a group of authors who we felt were extremely knowledgeable in given areas of allergy immunology and have asked them to share this knowledge with our readers. We presume that these readers will be physicians engaged in the "front line" care of the allergic patient. We have thus attempted to make this textbook as "user friendly" and clinical as possible.

The text is designed to give an overview of the principles of pathophysiology in such a manner as to allow them to be applied to the therapy of the patient. The major intent of the volume, however, is to help the physician deal with the day-to-day approach to the allergic patient.

The text is arranged to deal with individual disease states as well as the tools that we use to treat the allergic patient. Thus, there are chapters on common allergic diseases, such as asthma and rhinitis, as well as sections devoted to the drugs used to manage allergic patients and special techniques, such as allergen immunotherapy and environmental control.

In addition, controversial areas in our field are dealt with in a separate chapter written to familiarize the nonspecialist with forms of therapy that are, at best, of questionable value, and at worst no value at all. It is our hope that the text will disseminate some of the practical knowledge that we have accumulated over our three decades of practice and teaching. We also hope that its message has been delivered effectively, mainly to the primary care physician who is involved with the care of allergy patients.

Phil Lieberman, MD
John A. Anderson, MD

To Barbara
P. L.

and

To Nicole
J. A. A.

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1 Allergic Disease

Pathophysiology and Immunopathology

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INTRODUCTION

The primary care physician deals with allergic conditions far more often than he or she may suspect. Asthma, allergic rhinitis, and atopic dermatitis are just a few examples of these immunological diseases. The high prevalence of drug reactions in the population prompts all physicians to obtain an allergy history prior to prescribing any antibiotic, illustrating the importance of these disorders in clinical medicine.

With knowledge of the mechanisms mediating allergic reactions, a clinician can appreciate the pathophysiologic changes brought about by the introduction of a foreign antigen to a normally well-balanced system. This knowledge of the underlying mechanisms of allergic disease enables the physician to recognize and even 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 subsided.

The development of allergies involving IgE antibody formation, also known as **atopy**, involves both complex genetic and environmental influences that are only now being elucidated. Put simply, we cannot predict which individuals will develop allergies

From: *Allergic Diseases: Diagnosis and Treatment*
Edited by P. Lieberman and J. Anderson Humana Press Inc., Totowa, NJ

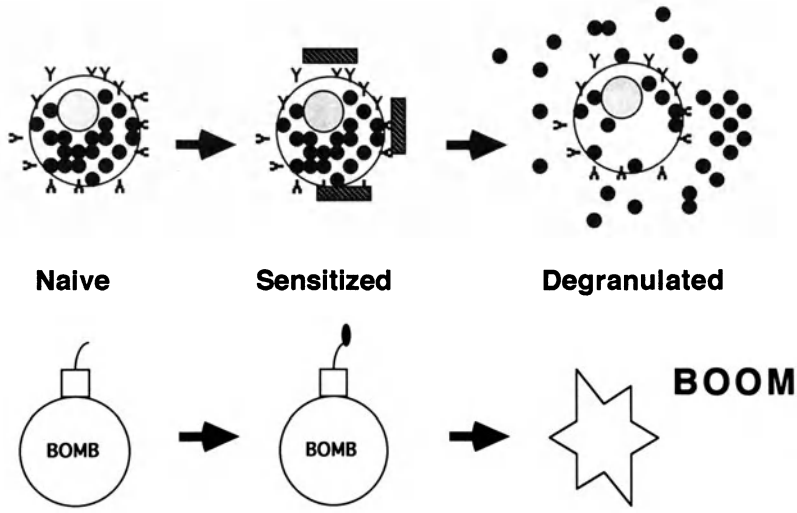

Fig. 1. Allergic sensitization and degranulation. The process of sensitization and degranulation in mast cells is analogous to the detonation of a bomb. Initial binding of specific IgE to the naive mast cell surface "primes" the cell for activity. Subsequent binding of allergen to the mast cell is akin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

and which will not based on simple Mendelian inheritance patterns. However, there does appear to be a higher incidence of allergies among offspring of allergic parents.

The two-step process by which one initially becomes "allergic" to a substance begins with **sensitization** (Fig. 1). During the initial stage of sensitization, the individual develops significant amounts of IgE antibodies against an inhaled, ingested, or injected substance. Memory B-cells that are capable of immediately producing more of this specific IgE antibody when stimulated also appear. The second stage involves the adherence of this newly formed IgE antibody to circulating blood basophils, or to the mast cell 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 considered to be "sensitized" only after IgE antibodies against a certain 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.

The second step in the two-step process of becoming allergic involves the re-exposure of a sensitized person to the allergen, with the production of symptoms ranging from negligible rhinorrhea to sudden death. Most cases lie somewhere in between. The biochemical events that lead to allergic symptoms will be discussed in some detail below, using an anaphylactic reaction to an insect bite as an illustrative example. How-

ever, 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 ALLERGIC REACTION: A SCENARIO

Six-year-old Jimmy Doe (John's son) was playing with toy trucks in his backyard, when he unwisely chose to bulldoze a yellow jacket nest. Fortunately, he escaped with a single bite on the ankle. While his mother was putting ice on the bite and wiping away Jimmy's tears, yellow jacket antigens, which were injected at the time of the bite, were being filtered through the bloodstream and the lymphatics, with some lodging in regional lymph nodes. Here the antigens encountered T- and B-cells and were recognized as foreign proteins. The interaction with lymphocytes leads to IgE production in those genetically predisposed—allergic or atopic individuals. This IgE was specifically directed against the yellow jacket venom, and circulated briefly through the bloodstream before binding to IgE receptors on 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 circulating antigen. By this time the venom had long since been cleared by the reticuloendothelial system, producing only a mild local reaction at the site of the sting. The only evidence that Jimmy was ever stung was the presence of the specific antivenom IgE on his mast cells and the presence of a few memory B-cells capable of producing more of the antivenom IgE if they were ever to see it again.

Two years later, Jimmy is stung again by a yellow jacket while at a picnic. Within minutes, he is wheezing and having difficulty breathing. He is gasping for air as the paramedics are summoned and is cyanotic by the time they arrive. Fortunately, prompt treatment allows him to recover. At a molecular level, the events responsible for Jimmy's problem began with the sensitization. From that point on, his immune system made him a living time bomb, ready to detonate when provoked by the yellow jacket antigen "trigger." Despite a two-year gap, the immune system never forgot its initial exposure to the venom. On being stung for the second time, the yellow jacket venom again circulated through the bloodstream and lymphatics. This time, however, it flowed past the mast cells with IgE antivenom antibodies already situated on their surfaces. These IgE molecules acted like molecular hands and grabbed the venom as it passed by. Eventually, when the number of venom molecules bound to the IgE on the mast cell surface became high enough, some of the IgE antibodies crosslinked and a chain reaction began. The mast cells poured forth preformed chemicals that had until then been quiescent in intracellular granules—chemicals that cause bronchoconstriction, vasodilatation, and upper airway edema. In addition, the triggering and degranulation of the mast cells led to the *de novo* production of other substances that also contributed to the reaction. The effect of the re-exposure to the venom in Jimmy's case is termed **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 immedi-

The Allergic Process

- The familial tendency to be allergic is called atopy.
- Children born to allergic parents, are born with the potential to be allergic, not with preformed specific allergies.
- Sensitization involves IgE antibody formation directed to specific allergens plus fixation to effector cells such as mast cells.
- Allergic reactions results from re-exposure to the allergen, allergen–IgE interaction at the cellular level, and release/formation of chemical mediators, which result in symptoms.

ate 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

As noted above, the key intermediary in allergic conditions is the IgE antibody. It is an individual's propensity to produce IgE in response to an "allergic antigen" (also known as an allergen) that renders him atopic. The same allergen that would stimulate B-cells to produce IgG or IgM in a nonallergic individual may stimulate IgE antibody production in an atopic person.

What makes the body respond to allergen exposure by making IgE as opposed to other classes of antibodies? You may recall that 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 (such as the nasal mucosa), whereas the IgG predominates in the bloodstream. Although all of the mechanisms by which a particular antigen favors the production of one class of antibody over another are not firmly established, 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 (against influenza virus, for example), but it will now be sitting on another constant region (IgG or IgA, for example). The process of class switching requires activation of the B-cells, a feat that is accomplished by B-cell interaction with helper T-cells. The T-cell utilizes direct cell-to-cell contact with the B-cell, as well as soluble cytokine signals. In the case of IgE production, the T-cell releases a cytokine called interleukin 4 (IL-4). This IL-4 reacts with the B-cell and seems to say, "switch to the IgE class of antibody." Indeed, 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. The molecular machinations responsible for these events are complex and beyond the scope of this chapter.

The ability to produce polyclonal IgE antibody is present as early as 8–10 wk of ges-

tation. Since IgE antibody cannot cross the placenta, any amounts present in cord blood have 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 their IL-4) to cease production of IgG or IgM and, instead, 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

The mast cell was first described by Paul Erlich in 1877, while he was still a medical student. He chose the name Mastzellen ("well fed") based on the cell's 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 $F_c\varepsilon RI$) on their cell surface. Despite gross morphological homogeneity, it is now apparent that mast cells are a heterogeneous cell population. Subtle histochemical differences are apparent when analyzing mast cell populations in different anatomical compartments. For example, mast cells isolated from the lung differ from those obtained from the skin. Most pulmonary mast cells primarily contain one neutral protease, called tryptase. Skin mast cells, on the other hand, contain large amounts of both tryptase and another protease, called chymase (described below). Mast cells in humans are divided and named based on this biochemical difference, and are termed MC_T or MC_{TC}, respectively. The tissue distribution of these subtypes of mast cells is illustrated in Fig. 2. The relative numbers of MC_T or MC_{TC} may change locally with tissue inflammation or fibrosis. It is thought that cytokine differences in the microenvironment of the tissues are responsible for this differentiation.

The most characteristic feature of the mast cell is undoubtedly the metachromatic granules, which account for over 50% of the cell volume and dry weight. These granules contain the preformed chemical mediators of allergic reactions, many of which are still unidentified. There are no accurate means of discerning from what tissue an isolated mast cell population is derived, since mixtures of both MC_T and MC_{TC} cells are found in all tissues. In other words, although a given tissue may display a predominance of one type of mast cell, the population is heterogeneous in all locations.

MEDIATORS OF THE ALLERGIC RESPONSE

The mediators released by the mast cells and the basophils can be grouped into two categories: the preformed substances contained within the granules and the newly gen-

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

Fig. 2. Distribution of human mast cell phenotypes. The relative distribution of the two predominant mast cell types, MC_T and MC_{TC} in immunologically relevant human tissues and cell populations. (Adapted from Holgate and Church. *Allergy*, London: Gower Medical Publishing, London, 1993.)

erated chemicals that are 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. Several representative mediators from each category will now be reviewed.

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 and smooth muscle spasmogenic effects. It can increase mucous 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. Similarly, localized vasoactive effects of histamine are seen in the "wheal and flare" reaction of a percutaneous allergen skin test.

Neutral proteases are compounds that catalyze the cleavage of certain peptide bonds in proteins, thereby facilitating 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**. Tryptase is found in both the MC_T and MC_{TC} subtypes of mast cells, whereas chymase is restricted to the MC_{TC} cells. Basophils have negligible, although detectable, levels of these proteases. The potentially dangerous proteolytic activity of these compounds is controlled by maintaining the interior of the granules at an acidic pH, thus inhibiting protease activity.

There are other accessory molecules that have prominent roles in the allergic response. **Proteoglycans**, including heparin and chondroitin sulfate A, are important in mast cell and basophil biochemistry, respectively. Both histamine and the proteolytic enzymes are bound to proteoglycan compounds within the granules. It is the proteoglycans that give the granules their distinctive crystalline structure. Their exact function is unclear, although many believe that proteoglycans stabilize the enzymes to which they are bound until degranulation occurs.

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; if dilatation is widespread, it can contribute to a lethal drop in blood pressure (shock)
		Increases permeability of small blood vessels	Swelling of local tissue; if change in permeability is widespread, it 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	Constrict 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 (from Lichtenstein, L. 1993, with permission).

There are two predominant classes of mediators that are synthesized *de novo* following activation of the mast cells and basophils: the lipid derivatives and the cytokines. The lipid derivatives include the **leukotrienes** and the **prostaglandins**. They represent byproducts of the metabolism of arachidonic acid formed on 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 (which was generated by phospholipase A_2 acting on cell membrane constituents), demonstrate many different activities, of which the most prominent is an 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.

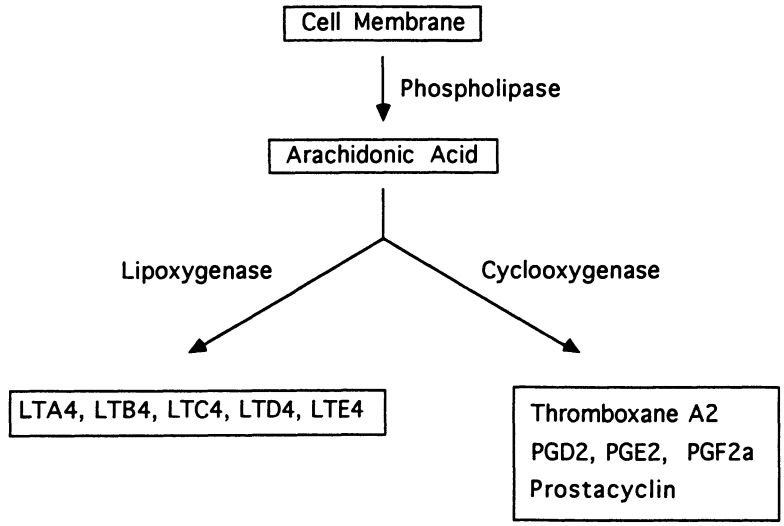

Fig. 4. Arachidonic acid metabolic pathways. Arachidonic acid, released as a result of phospholipase action on the cellular membrane, is broken down by two distinct biochemical pathways. The lipoxygenase pathway results in formation of the leukotrienes, whereas the cyclooxygenase pathway generates prostacyclin,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

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

The identification of the **cytokines** synthesized by mast cells and basophils is currently an area of intense investigation. Cytokines represent the primary mechanism by which cells can influence the activity and development of unrelated cells. In addition, many cells respond in an autocrine fashion to the cytokines they, themselves, secrete. Although most mast cell cytokine studies have been performed in rodent cells, several cytokines have been identified in human mast cells. We know that human mast cells produce IL-4 and interleukin 5 (IL-5) as well as tumor necrosis factor alpha (TNF-α). The IL-4 stimulates mast cell differentiation and promotes immunoglobulin class switching to the IgE isotype. Interleukin-5 is the most important factor involved in eosinophil production and survival in humans. The TNF-α increases vascular permeability and leukocyte migration.

Basophils have long been incorrectly viewed as the "blood-borne" equivalent of mast cells with analogous granules and functions. However, these cells represent a hematopoietic lineage distinct from mast cells, 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, prostaglandin D_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 elevated

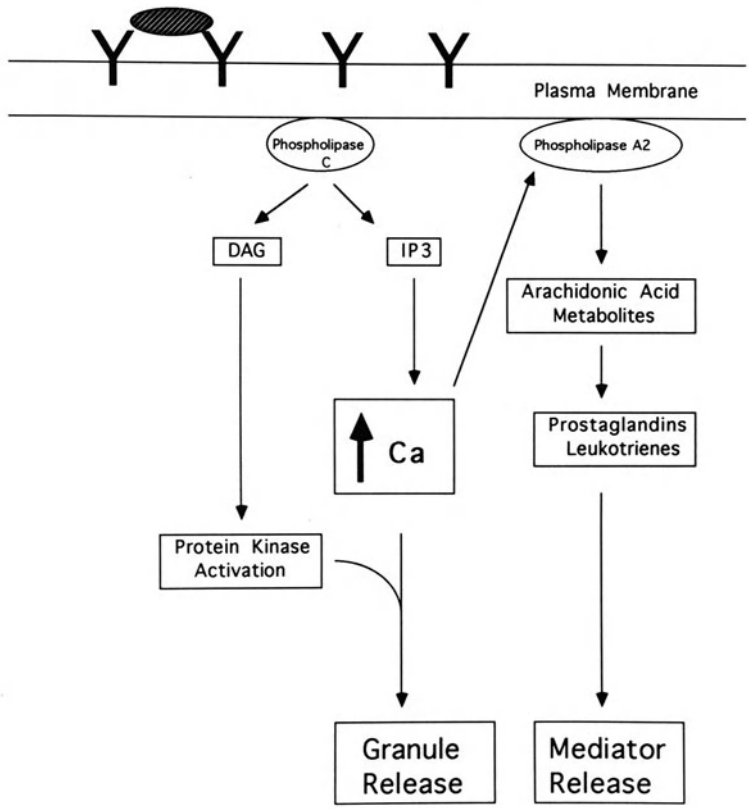

Fig. 5. Mast cell activation: biochemical reactions. Following IgE crosslinking by antigen, a series of protein kinase reactions culminate in the activation of phospholipase C, releasing DAG and IP_3 from the plasma membrane. The IP_3 releases calcium stores from the endoplasmic reticulum, which, along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

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. Although immensely complex, a basic appreciation of the process will prove useful in understanding the nature of the allergic response. An overview of the reactions is illustrated in Fig. 5.

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. It is important to remember that there are thousands of different IgE molecules on every mast cell—each of which is capable of binding to a different antigen. They float about freely on the mast cell surface, bound by the F_c portion of the IgE, until they bump into the ap-

propriate antigen, at which point they bind tightly. Once bound by one IgE molecule, there is a strong possibility that other IgE molecules with similar specificities will also attach themselves to the antigen. It is at this point, with the antigen attached to the mast cell by more than one IgE molecule, that a cytoplasmic "shiver" travels through the cell, causing activation. This "shiver" is an oversimplification of a process 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 $F_c\varepsilon RI$ 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). A series of phosphorylation cascades begins the process. This is nature's way of conserving energy—charged phosphate molecules are transferred between different compounds (usually tyrosine or serine amino acids on proteins) using enzymes called kinases. Eventually, a protein called phospholipase C becomes phosphorylated and moves from the cytosol to the membrane, where it assumes an active conformation. This protein catalyzes the release of inositol triphosphate (IP_3) and diacylglycerol (DAG) from the mast cell membrane. The IP_3 causes release of calcium from intracellular stores in the endoplasmic reticulum, whereas DAG is used to activate proteins involved in granule release. The calcium serves two central functions: It is used as a cofactor for the release of the granules (with the DAG), and also it serves to activate a protein called phospholipase A_2 (PLA_2), the regulator of lipid mediator production. In summary, at this point, we have the mast cell able to release granules, but the other effector function, that of prostaglandin and leukotriene production, is just beginning.

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, an integral membrane component. In turn, arachidonic acid is formed and metabolized via the two pathways mentioned 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 an 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 in order to achieve a crosslink, which is possible only if sensitization had occurred previously.

Allergic (IgE-mediated) activation of the mast cell is summarized above, 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 nonimmunologic degranulation may be triggered by opioids, anaphylatoxins (complement components), or even radiological contrast dyes. Indeed, 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 prompt 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 of Jimmy Doe, our youngster sensitized and subsequently stung by a yellow jacket, 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 considering the muscles surrounding the bronchial airways; and increased glandular mucous secretion, an annoyance in the nasal mucosa but dangerous in the small bronchioles. Extreme 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 <1 min, but the lipid mediators are slowly metabolized. As you recall, both leukotrienes and prostaglandins are only synthesized after an allergic reaction has begun, thus accounting for the delay in onset of action. 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.

EARLY- AND LATE-PHASE RESPONSES

An important aspect of allergic disease, with clinical as well as scientific 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—from the signal transduction pathways to the presence of granules containing preformed, "ready-to-use" mediators. 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 com-

Early vs Late-Phase Allergen Reactions

Early	*Late*
• Clinical response to stimuli within minutes and up to 2 h	• Response to stimuli in 2–8 h, usually following an early reaction
• Predominant effector cell: mast cell	• Predominant effector cell: basophil
• Predominant mediators include histamine, chemotactic agents, prostaglandins (PG), and leukotrienes	• All mediators, except PGD_2 plus platelet activating factor (PAF)
• Cellular response—sparse, if any	• Cellular response marked—eosinophils, neutrophils, and mononuclears

pletely 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. As stated above, the LAR represents the inflammatory phase of an allergic reaction, no matter where in the body it occurs. Subtle differences in the nature and effect of the mediators involved in the LAR have been observed in each anatomical location where it has been described. We will consider three such microenvironments: the skin, the nose, and the lungs.

The **cutaneous** early reactions are well described. These are the characteristic "wheal and flare" reactions 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, actually blending into a late-phase response that peaks at 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, since, in contrast to the mast cells, 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).

The **pulmonary** LAR probably has received the most attention of all anatomical sites, probably owing to the increasing frequency and severity of asthma in the population. In the lung, the pattern of allergic responses is well defined, with numerous examples of solitary early responses and solitary late responses, as well as dual responses (*see* Chapter 7). Clinically, isolated immediate responses are those that cause airway obstruction (with wheezing, coughing, or shortness of breath) within minutes of allergen exposure. They typically resolve within 1 h. Late-phase reactions begin 3–4 h after allergen exposure and resolve within 24 h. The symptoms associated with the late response are similar to the immediate response, with dyspnea and cough predominating. The pulmonary dual response consists of both the early and late response, separated by an asymptomatic interval of normal baseline pulmonary function. In addition to typical aeroallergens, exercise has also been shown to elicit a dual response in some individuals.

The mediators released during an early allergic response summon more helper ($CD4^+$) T-cells that, in turn, send out cytokine signals that attract other diverse cell types to the area. Among these cytokines are IL-4, which serves to increase IgE production, and IL-5 and GM-CSF, which increase eosinophil production and survival. In addition, other cytokines serve to increase the expression of specific leukocyte receptors on endothelial cells lining the pulmonary vasculature, thus facilitating transmigration of these cells from the bloodstream into the airway lumen.

SUMMARY

In summary, it is evident that several generalities apply to all tissues in which an allergic reaction can occur. The early phase response, the immediate result of an interaction between a sensitized mast cell and a specific allergen, results in the release of preformed mediators, which exhibit both local and distal target organ effects. The cellular effects of these mediators is similar in each tissue, but 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 tissues and represents the inflammatory response. Since the goal of the late-phase response is to attract inflammatory cells, the cytokine profile differs slightly from the immediate response.

How does all this relate to little Jimmy Doe, our unfortunate youngster with allergies to yellow jackets? His primary care physician wisely sent Jimmy to a specialist, where he completed a course of immunotherapy, and has enjoyed care-free summers since then. 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

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CONTENTS

INTRODUCTION

Allergic diseases are among the most common conditions treated by physicians. It is estimated that up to 20% of the population has or will have an allergic condition, such as allergic rhinitis, allergic conjunctivitis, asthma, atopic dermatitis, urticaria, and food or drug allergy. In approaching the evaluation of the patient with suspected allergy, it is important to elicit a detailed medical history, perform a comprehensive physical examination, and obtain appropriate diagnostic tests.

HISTORY

The most important part in evaluating the patient with possible allergic disease is the medical history. It is from a complete history that appropriate physical examination and laboratory tests develop. The allergic medical history includes all the major topics covered in medicine or pediatric histories, along with a detailed environmental evaluation. Because many conditions may mimic allergy, it is just as important for the history to pursue this possibility. Many allergists have patients complete detailed questionnaires prior to their office visit (Fig. 1). This procedure can be helpful in allowing the patient to gather information for the physician, to ensure that no important detail is omitted. Other physicians use an allergy questionnaire in the office while obtaining the history.

First, the chief complaint is established. This is the starting point for the proper questioning of the patient. If the chief complaint is specific, such as "I have fall hay fever," the history can be oriented for this condition. A nonspecific chief complaint requires probing questions to define the problem clearly. The present history should elicit all the

From: *Allergic Diseases: Diagnosis and Treatment*
Edited by P. Lieberman and J. Anderson Humana Press Inc., Totowa, NJ

Allergy Questionnaire

Patients' Name: Date of Birth:

Referring Physician:

1. Describe briefly the reason for your visit to the allergist and what you hope to accomplish:

2. Problems:

Yes	No	Check all items	Age of Onset	Severity MILD	Severity MOD.	Severity SEV.	Comments
		Asthma (Wheezing)					
		Sinus Trouble					
		Hay Fever					
		Hives or Swelling					
		Eczema or other rashes					
		Frequent Infections					
		Food Reactions					
		Drug Reactions					
		Insect Reactions					

3. Symptoms: Have you had any of the following? If no, leave blank.

	How many days in the last month.	Severity MILD	Severity MOD.	Severity SEV.	Which months are the worst?
Runny or stuffy nose					
Itchy nose					
Sneezing					
Itchy eyes					
Wheezing					
Coughing					
Wheezing or cough with exercise					
Skin problems					

4. Food reactions

Food: Approximate Date: Symptoms:

5. Precipitating factors/triggers.

Circle all the following which trigger symptoms:

a. Cutting or playing in grass

b. Raking leaves

c. High winds

d. Other outdoor exposure

e. Moldy/mildew areas (basement, etc.)

f. Smog, smoking, or smoke exposure

g. Sweeping, dusting, or vacuuming

h. Air conditioning or heat

i. Cleaning agents, soaps, bleach

j. Paint, perfume, chemicals, cooking odors

k. Exposure to animals

l. Physical exertion

m. Cold weather

n. "Colds" or viruses

6. Previous Allergy Evaluation and Therapy

Have you ever had allergy skin tests? If yes, give date and results of tests

Have you ever had allergy injections? If yes,give date and length of treatment

List all medications you are presently taking; include dosage and number of times per day:

List all previous medications you have taken for allergies:

7. Hospitalizations

List all hospitalizations, reason for hospitalization and date:

8. Surgery

List all surgeries, reason for surgeries and date:

9. Family History

Do any member of your family have a history of allergy?

	Yes	No	If yes, list all relatives
Asthma			
Hay Fever			
Eczema			
Hives			
Swelling			
Frequent Infections			
Other allergies			
Cystic Fibrosis			
Emphysema or other lung diseases			

10. Smoking Survey

Do you presently smoke? If yes for how many years and average packs per day

Fig. 1. *continued*

Have you ever smoked? If yes, for how many years and average packs per day

How many other family members who live in the same house smoke?

11. Environmental Survey

a. Do you live in a house, trailer, or apartment? Age of house?

b. Do you have any rooms that are damp or musty?

c. Has the house ever been flooded?

d. List the types of air conditioning and heating system in your home.

e. Do you have an air cleaner or air humidifier?

f. Is there carpet in your bedroom? Wall to wall or area?

g. Is there a fan in your bedroom?

h. Are there any feather objects in your bedroom, such as pillows or comforters?

i. What type of mattress do you have?

j. What kinds of grasses, trees, and shrubs are in the near vicinity of your house?

k. Do you have any pets? If yes, list the types of pets and are they indoors at anytime?

l. What type of work do you do?

m. Are you exposed to anything at work or school that might aggravate your condition?

n. How many days from school or work have you missed in the last year because of your allergies?

o. Do you have any other exposures from hobbies or other recreational activities which aggravate your condition?

p. If the patient is a child, where is he/she during the day? If in day care, please the specific number of years in day care and number of children in the day care your child attends?

Fig. 1. Allergy questionnaire. Modified from the National Jewish Center for Immunology and Respiratory Medicine, Denver, CO.

patient's current symptoms. Typical symptoms associated with allergic rhinitis include repetitive sneezing, nasal itching, and clear rhinorrhea. Asthmatic patients may have chronic cough, wheezing, chest tightness, and shortness of breath.

Many allergic conditions, such as asthma, urticaria, and allergic rhinitis, appear only at certain times of the year or in specific locations. It is important for the physician to know the times of year that particular outdoor allergens are in the air. Pinpointing the season of the year during which symptoms occur can often lead to an accurate diagnosis of the offending allergens. Even when symptoms occur year-round, there may be certain seasons when symptoms are worse. Depending on the area of the country, certain outdoor allergens occur at particular times of the year. In many areas of the United States, weeds pollinate in the fall, trees in the early spring, grasses in the late spring and early summer, and mold spores in the summer. In certain regions of the southern United States, mold spores and grass pollens can be a year-round allergen.

Increasingly, indoor allergens are contributing to more allergic disease. House dust mite and cockroach allergies can cause perennial symptoms, although they may be worse in the winter when forced-air heating stirs up these allergens. Dust mites have their highest concentration in the carpet and bedding, especially in feather objects, such as pillows and comforters. Many patients with dust mite allergy exhibit symptoms on arising in the morning, such as repetitive sneezing and other nasal problems. Animal allergens can also play a major role in allergic diseases. Cats are now the number one indoor animal in homes in the United States. These animals in general are more allergenic than dogs and can trigger major allergy symptoms. In addition to cats and dogs, it is important to determine if there are any other animals in the house, such as birds, gerbils, rabbits, and hamsters. Mold spores can trigger allergic reactions both indoors and outdoors. Are there moldy areas in the home? Homes with basements or that have been flooded may have high levels of mold spores in the air. Also, homes with numerous potted plants may have high levels of mold spores in the environment owing to fungi growth in the soil. Do the patient's symptoms worsen when a live Christmas tree is in the house? This could be owing to mold spores on the tree.

Irritants in the environment may be provoking symptoms in the patient. Does the patient smoke or is he or she exposed to passive smoke? Although cigaret smoke is not an allergen, it has been linked to worsening allergic symptoms and triggering of asthma in children. Wood burning stoves, fireplaces, and kerosene heaters may also provoke respiratory symptoms in the allergic patient. Children in day care centers may have twice as many upper respiratory infections per year compared to children who stay at home. Many times these children are mistakenly thought to have allergic conditions.

Where symptoms occur can lead to the discovery of the allergic cause. Are symptoms occurring at work or school? Many occupations involve exposure to particular allergens, such as baker's asthma resulting from flour, allergic rhinitis and asthma from exposure to natural rubber latex in health care workers, and laboratory workers with allergy to laboratory animals. In children, are symptoms worse during the school week or the weekend? Are there any differences in symptoms in different geographic locations? Do the patient's symptoms improve when they are on vacation? Are symptoms better or worse at someone else's house? These questions could give information useful in narrowing down the type of allergens that may be contributing to the patient's symptoms.

The history is the most important element in the evaluation of the allergic patient. 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; and
- The presence of associated allergic conditions.

Because many patients with one type of allergic disorder also have other allergic conditions, a detailed review of systems is required. Patients with asthma may have allergic nasal and eye symptoms. Are there skin manifestations, such as atopic dermatitis, urticaria, and angioedema? If urticaria or hives are present, how long has the patient had this condition? Acute urticaria is hives that have been occurring for <6 wk. Common causes of acute urticaria are foods, drugs, inhalant allergies, contacts, or insect stings. Patients with hives for longer than 6 wk have chronic urticaria. One should question the patient with chronic urticaria about foods, drugs, contacts, infections, physical conditions, and chronic diseases, such as malignancies, autoimmune, and endocrine disorders.

An idea of the severity of the condition can be obtained by questioning the patient about the number of days of school or work that have been missed, the number of emergency department visits, and hospitalizations. Because allergic conditions are usually chronic, many patients have had previous evaluation and treatment for their problems. This information can be helpful in diagnosis and management of the patient. Has the patient had previous allergy testing? How were the tests done, and how long ago were they done? Depending on whether proper methods of allergy testing were used, this could give data on possible allergens. Since children may develop new allergen sensitivities as they grow older, previous testing may not be valid. Were any other diagnostic studies done in the past, such as pulmonary function studies, serum IgE, RAST, chest, or sinus roentgenograms? Did the patient have allergen immunotherapy injections in the past? If injections were not successful, it may have been too short a duration of treatment or may have been too low strength of the allergenic material. What medications has the patient used for the allergic conditions? Were these medications helpful or not, and were there any side effects? This information gives the physician important data in determining what medications should be avoided and possible future treatment.

Family history is helpful in evaluation of the patient, since heredity plays a major role in the development of allergy. It is estimated that 40–80% of allergic patients have a family history of allergic disease. Pertinent family members are the parents, grandparents, and siblings. Of course, a negative family history for allergies does not rule out an allergic condition. It is important in obtaining the family history to inquire about conditions that may mimic allergic disorders, such as cystic fibrosis and immune defects.

PHYSICAL EXAMINATION

A major component in the comprehensive evaluation of the allergic patient is the physical examination. In many patients in whom allergic symptoms are intermittent, the physical examination may be entirely normal when the patient is first evaluated. This should not steer the physician away from the possibility of allergy. In children, it is important to document growth, since growth is delayed in the severely asthmatic child. Also, children on chronic oral corticosteroids may have growth suppression. Increased heart and respiratory rate and pulsus paradoxus may be seen during an acute asthma episode. Pulsus paradoxus is a >10 mmHg difference in systolic blood pressure during inspiration and expiration.

Eye examination should concentrate on the conjunctiva. In allergic conjunctivitis, there is periorbital edema, conjunctival injection, chemosis, and excessive tearing with a white ropy discharge. "Allergic shiners," dark swelling under the eyes, are seen in many patients with allergic rhinitis (Fig. 2). A groove under the lower eyelid, "Dennie's line," is observed in many patients with allergic disorders. Examination of the tarsal conjunctiva may reveal "cobblestoning," seen in patients with vernal conjunctivitis, atopic keratoconjunctivitis, and giant cell conjunctivitis. Patients with chronic atopic dermatitis for several years may develop cataracts.

Otitis media with effusion is commonly present in children with allergic rhinitis. Pneumatic otoscopic examination of the ear should be performed to evaluate the middle ear for the presence of fluid or infection.

One of the major organs involved in allergic disease is the nose. Many patients with allergic rhinitis continually rub their noses. This can lead to the development of a "nasal crease," a transverse groove across the bridge of the nose (Fig. 3). Examination of the nose can be performed with an otoscope or a head mirror with a nasal speculum. Looking at the nasal septum will determine if it is deviated. If a nasal septal perforation is observed, it is important to consider cocaine abuse. The inferior turbinates are usually easy to evaluate. In many patients with allergic rhinitis, the turbinates are usually pale blue in color, swollen, and show serous drainage. In vasomotor rhinitis and viral rhinitis, the turbinates are usually inflamed with mucoid drainage. It is important to check for nasal polyps, grayish white grape-like growths, which may be seen in patients with allergic rhinitis, aspirin sensitivity, and cystic fibrosis.

The frontal and maxillary sinuses may be palpated to determine tenderness, which can occur with acute sinusitis. Transillumination of the sinuses may be helpful in evaluating sinus disease in adults, but is usually not accurate in children. On nasal examination, purulent drainage from the sinus ostia indicates infection in the sinuses. Examination of the throat should check for chronic postnasal drip and associated posterior pharnygeal cobblestoning.

Chest examination starts with observation of the configuration of the chest. In patients with asthma, there may be an increased anterioposterior diameter owing to air trapping. During the acute asthma episode, there is an increased respiratory rate with use of accessory muscles, such as the intercostals and the sternocleidomastoids. Percussion of the chest of the asthmatic may elicit a hyperresonant sound resulting from hyperinflation. On auscultation of the chest, the asthmatic commonly has a prolonged ex-

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

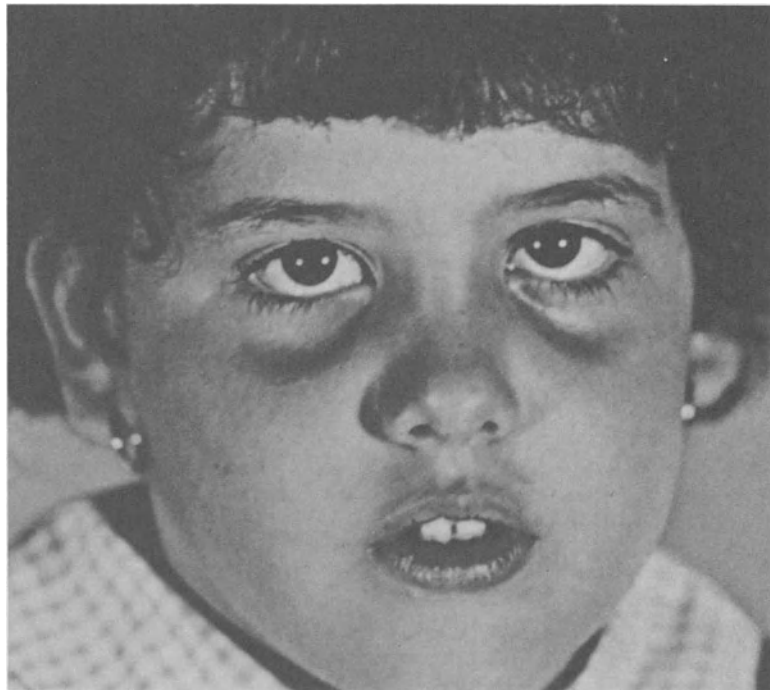

Fig. 2. Allergic shiners in a child with allergic rhinitis. Reprinted by permission of the American College of Allergy, Asthma, and Immunology in Stigmata of Respiratory Tract Allergies, The Upjohn Company, Meyer B. Marks, ed., copyright 1991 from page 14, Fig. 13.

piratory phase with diffuse inspiratory and expiratory wheezing and rhonchi. In a severe asthma exacerbation with widespread bronchial obstruction and mucous plugging, a "silent chest" without wheezing may be present. Many asthmatic patients who are symptom-free may have a normal chest examination, whereas others even when "feeling normal" may have wheezing, especially on forced expiration.

Another organ system commonly involved in allergic disorders is the skin. Atopic dermatitis occurs in about 10% of the population. The physical findings in atopic dermatitis depend on the age of the patient and the stage of the disease. In infants, the pruritic lesions are usually erythemic and oozing, and located on the cheeks and the extensor surfaces of the arms and the legs. Over time, the lesions develop a more macular papular character with vesicles. In the older child and adult, the lesions become increasing crusted and thickened with the typical locations being the neck, ankle, and the antecubital and popliteal fossae. Urticaria, or hives, are pruritic raised erythemic lesions

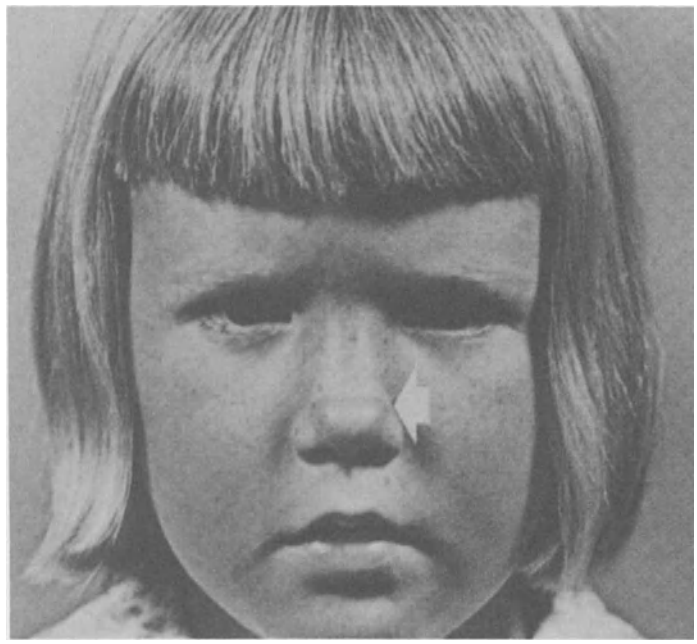

Fig. 3. Transverse nasal crease in a child with allergic rhinitis. Reprinted by permission of the American College of Allergy, Asthma, and Immunology in Stigmata of Respiratory Tract Allergies, The Upjohn Company, Meyer B. Marks, ed., copyright 1991, from page 13, Fig. 10.

The most important ancillary test to confirm the diagnosis of allergy is the skin test, which is the "gold standard" in this regard. The skin test results must be interpreted in light of the history to determine the importance of a positive test.

with a pale center that occur in about 10% of the population at some point in their lives. Many of these patients have associated dermatographism, which is a wheal and flare reaction that occurs on scratching the skin.

LABORATORY STUDIES

Laboratory tests are commonly used in evaluating patients for allergic disorders. Complete blood counts may show an eosinophilia (>7%) in patients with asthma and other allergic conditions. Otherwise, no other blood abnormalities are commonly seen. Nasal smears for eosinophils may be helpful in the assessment of the patient with nasal problems. In patients with allergic rhinitis, there are commonly >10 eosinophils/high-power field. The absence of eosinophils does not rule out allergic rhinitis, and a positive eosinophil smear can be seen in patients with nonallergic rhinitis with eosinophils (NARES Syndrome). Urinalysis, sedimentation rate, and blood chemistries are usually normal in patients with allergies. Examination of the stool for ova and parasites may be

helpful in patients with eosinophilia and elevated IgE and no evidence of allergic disease, or in patients with unexplained chronic urticaria and angioedema. Chest roentgenograms are mandatory in all patients having an initial workup for asthma, and sinus roentgenograms are frequently needed in many patients with symptoms of chronic nasal and sinus disease to document sinusitis.

SKIN TESTING

IgE is the primary antibody in allergic reactions. Many of the tests used in diagnosing allergic disease center on detection of this antibody. The gold standard in determining specific allergens to which the patient may have clinical sensitivity is allergen skin testing. In patients with a sensitivity to a particular allergen, there are IgE antibodies to this allergen on the mast cells in the skin. When the allergen is introduced into the skin, it will bind to the IgE antibodies, triggering the release of chemical mediators from the mast cells. These chemical mediators, such as histamine, lead to a characteristic wheal and flare reaction. These reactions usually develop over 10–15 mins. It is important to note that a positive allergy skin test does not mean that the allergen is causing the patient clinical symptoms. Therefore, one must correlate the allergy skin test results with the clinical history in order to determine if the allergens are truly relevant to the patient's condition.

Allergen skin tests are commonly used to detect allergy to inhalants, foods, certain medications (i.e., penicillin), and hymenoptera venoms. Figure 4 illustrates the allergy skin test sheet used at the University of Tennessee.

IN VITRO TESTS

Techniques are available to measure both total and specific serum IgE levels in patients. Total serum IgE levels are performed by either radio- or enzyme immunoassays. IgE is measured in international units (1 IU = 2.4 ng IgE). Serum IgE levels are age-specific, with umbilical cord levels at <0.5 IU, which increase to 200 IU around puberty, but then slowly decrease in adults to around 150 IU. Unfortunately, total serum IgE levels are not a reliable indicator of allergic disease. Some patients with high levels are not atopic and vice versa. Measuring total serum IgE levels may be helpful in infants. Umbilical cord levels of >1.0 IU are a good predictor of whether the child will develop allergic disease. Another indication for measuring total serum IgE levels is the suspicion of allergic bronchopulmonary aspergillosis. With treatment of this condition, IgE levels fall, whereas exacerbations lead to higher serum IgE levels.

The major in vitro test for measuring specific IgE to an allergen is the RAST, or radioallergosorbent test. There are several modifications of this procedure, but in general, it is a two-step approach in which allergen is bound to a paper disk and incubated with the patient's serum. If IgE antibody to the particular allergen is present, it will bind to the allergen–disk complex. Next, the IgE–allergen–disk complex is washed and incubated with a radio-tagged or enzyme-linked anti-IgE and assayed for levels of specific IgE. The main advantages to this test over allergen skin testing are that there is no risk of systemic reaction or interference of results from medications. It can

MEDICAL GROUP

Allergy Skin Test Record

PR (Prick test)
ID (Intradermal test)

ALLERGEN	PR	ID	ALLERGEN	PR	ID	ALLERGEN	PR
ENVIRONMENTALS			**MOLD SPORES**			**FOODS**	
Cat Dander			Alternaria			Wheat	
Cockroach			Aspergillus			Egg	
Dog Dander			Curvularia			Milk	
Dust Mite (D.farinae)			Fusarium			Peanut	
Dust Mite (D. ptero)			Helminthosporium			Chocolate	
			Cladosporium			Soybean	
TREE POLLENS			Penicillium			Corn	
Maple			Phoma			Chicken	
Cottonwood			Stemphyllium			Pork	
Elm						Beef	
Birch						Shrimp	
Oak			**CONTROLS**			Oyster	
Pecan			Histamine			Cod fish	
Sycamore			Control			Tomato	
Willow						Orange	
Ash						Catfish	
						Potato	
GRASS POLLENS						Yeast	
Bahia						Oat	
Bermuda						Pecan	
Johnson						Apple	
June/Kentucky						String Bean	
Rye						Onion	
Timothy						Rice	
WEED POLLENS							
English Plantain							
Kochia							
Pigweed							
Giant Ragweed							
Short Ragweed							

Fig. 4. Allergy skin test record.

also be used in patients with severe skin disease or dermatographism. The disadvantages over skin testing are variations in the quality of the test, interference with high total serum IgE levels, much higher cost, and results of the test not being immediately available.

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3 Diagnostic Tests in Allergy

Dennis R. Ownby, MD

CONTENTS

INTRODUCTION

Many physicians have the mistaken impression that allergic disease is diagnosed by allergy testing. The diagnosis of allergic disease is primarily dependent on the patient's history of signs and symptoms typical of allergic disease during or shortly after allergen exposure. A common clinical example is a patient who states that every time he or she visits a home with a pet cat, he or she develops red, itchy eyes and sneezing. The ocular and nasal symptoms are typical of allergic disease, and the onset of symptoms when in homes with pet cats suggests that the symptoms are related to exposure to cat allergen. Two additional factors to consider when evaluating a history are the number of times the patient has noted the association between allergen exposure and symptoms, and whether similar symptoms occur at other times. If the symptoms are exclusively related to cat exposure and have occurred on multiple occasions, the diagnosis is relatively certain. The final step in confirming a diagnosis of cat allergy would be demonstration that the patient has detectable cat-specific IgE antibodies.

To clarify further the role of allergy tests in the diagnosis of allergic disease, it is useful to define a "gold standard" for diagnosis (*see* Table 1). To be certain that a patient has an allergic disease, it would be necessary to demonstrate that exposure to the putative allergen, under double-blind, placebo-controlled conditions, produces signs and symptoms of the disease process in question. It would also be necessary to demonstrate that the signs and symptoms are the result of chemical mediators released from mast cells and basophils via IgE binding to the allergen. This stringent definition of allergic disease is rarely met, even in research studies, because performing allergen challenge is very difficult.

From: *Allergic Diseases: Diagnosis and Treatment*
Edited by P. Lieberman and J. Anderson Humana Press Inc., Totowa, NJ

Table 1
Criteria for Diagnosis of Allergic Disease

1. Absolute criteria for diagnosis of allergic disease (the Gold Standard)
Reproducible symptoms occurring during double-blind, placebo-controlled, allergen exposure when the route, dose, and duration of allergen exposure are consistent with estimated or measured natural or occupational exposure, and
The observed symptoms must be the direct result of the release of chemical mediators when the release of the mediators is triggered by the binding of IgE antibodies to the allergen
2. Clinical criteria for diagnosis of allergic disease
A history of signs and symptoms typical of allergic disease at a time and place when allergen exposure is probably occurring, and
The demonstration that the patient has IgE antibodies specific for the allergen associated with the occurrence of symptoms

Because of the difficulty in trying to satisfy the criteria of the gold standard, clinical criteria are usually accepted for diagnosis of allergic disease. Clinical criteria vary to some degree depending on the clinical situation and the relative risks and benefits to the patient, but usually include a history of recurrent symptoms of allergic disease when allergen exposure is occurring and the demonstration of allergen-specific IgE antibodies (Table 1). Thus, allergy tests are only adjuncts to the clinical diagnosis of allergic disease. There is a great temptation to equate the presence of detectable allergen-specific IgE antibodies with the diagnosis of allergic disease, but many individuals with antibodies are asymptomatic. In fact, some studies of large, relatively unselected populations have shown that over 90% of persons with IgE antibodies to stinging insect venom have no history of allergic reactions from insect stings. It is very important to understand that tests for allergen-specific IgE antibody, whether skin tests or in vitro tests, have little clinical value unless they can be interpreted in association with the patient's clinical history.

SKIN TESTING FOR DETECTION OF ALLERGEN-SPECIFIC IGE

Physiology of Skin Tests

Skin tests are performed by introducing a small quantity of allergen into the epidermis by pricking, puncturing, or scratching the skin or by intradermal injection. The immediate wheal and flare response resulting from a skin test is the result of a complex series of interactions. After the allergen has been introduced into the skin, the allergen diffuses through the skin and interacts with IgE antibody bound to mast cells. Binding of the allergen to IgE antibodies bound to mast cells initiates the release of preformed (histamine, tryptase, chymase, heparin) and newly synthesized (prostaglandins, leukotrienes, cytokines) mediators.

The central wheal of the skin response is the result of histamine-induced vasopermeability and secondary edema. The central erythema results from histamine-induced arteriolar vasodilation, and the circumferential erythema results from the stimulation of nerve receptors and a resulting axon reflex vasodilation. The wheal and flare responses

are typically maximal at 15 min after introduction of the allergen. Most of the visible skin response to an allergen can be blocked by an H_1 receptor antagonist (antihistamine), but complete inhibition requires both H_1 and H_2 antagonists.

Following the immediate skin response, and depending on the dose of allergen and the sensitivity of the patient, there may be a late-phase reaction (LPR). LPRs usually begin 3–5 h, peak at 6–12 h, and resolve approximate 24 h after the immediate response. Clinically, LPRs are characterized by pruritus and edema often larger than the immediate reaction. Pathologically, LPRs are characterized by infiltration of inflammatory cells, including neutrophils, monocytes, and esosinophils. Fibrin deposition also occurs. LPRs may complicate immediate skin testing and may be the mechanism responsible for large local reactions following administration of allergen immunotherapy injections.

Evaluation of Patient Prior to Skin Testing

Before skin testing, a patient must be evaluated by an experienced physician. Beyond establishing the likelihood of allergic disease, a patient's history and physical examination should alert the physician to any unusual risks of skin testing. Skin testing is generally safe, but skin tests always carry a risk of inducing a systemic allergic reaction (anaphylaxis), which could be life-threatening. Anything that might increase the risk of skin testing for a patient must be evaluated before skin testing. Emergency equipment to treat anaphylaxis must always be immediately available when patients are skin tested. Since epinephrine is the drug of choice for treatment of major allergic reactions, drugs altering the response to epinephrine, such as β-blocking agents, should be discontinued prior to skin testing. Pregnancy is a relative contraindication to skin testing, because the fetus *in utero* may be highly vulnerable to hypoxia during a systemic reaction in the mother. Patients with chronic medical problems, such as severe lung disease or unstable angina, should not normally be skin tested. Finally, patients with current, severe allergic symptoms, especially unstable asthma, should not be skin tested until after their symptoms have been stabilized because of a greater risk of systemic reactions.

In addition to general medical concerns, the physician supervising skin tests must be sure that the patient has an area of normal skin suitable for skin testing. Patients must not be taking antihistamines or drugs with antihistamine actions, such as tricyclic antidepressants, because these agents can attenuate skin test responses. Patients with severe skin disease or with marked dermatographism cannot be reliably tested. Both the very young and the very old have less reactive skin, and criteria for grading skin test reactions need to be adjusted in these individuals. Following viral exanthems or sunburns, the skin may not be normally reactive for several weeks, and skin testing should be postponed.

Epicutaneous Skin Tests

Percutaneous or epicutaneous tests may be performed using a variety of methods, but the most common methods are the prick and puncture techniques. The prick test is performed on previously cleansed skin by passing a small needle (e.g., 25- or 26-gage) through a drop of allergen extract at approximately a 45° angle to the surface of the skin. The needle is lightly pressed into the epidermis, and the tip of the needle is then lifted up

Allergen Skin Testing Precautions

- The individual to be tested must be off usual conventional antihistamines for 24 h, Loratadine, and Hydroxyzine for 5 d, and astemizole for 6–12 wks.[a]
- Tricyclic antidepressant drugs often have profound "antihistamine effects" and usually preclude allergy skin testing.[a]
- Use of β-blocker drugs (e.g., for hypertension or migraine headache) increases the risk of a serious reaction if a reaction to an allergy skin test occurs.[a]
- Allergy skin testing should not be performed when the patient is acutely ill, including an acute asthma attack or with generalized skin rash.[a]

[a] Alternative in vitro IgE allergen-specific skin testing should be considered.

producing a pricking sensation. The skin pricks should not be deep enough to produce visible bleeding.

Another epicutaneous method is the puncture technique. A drop of allergen extract is placed on cleansed skin. A puncture device is then pushed into the skin though the drop of extract. Commonly used puncture devices are constructed to allow a small point to penetrate 1–1.5 mm into the skin. Further penetration is prevented by the instrument's shape. The bifurcated needle, originally designed for smallpox vaccination, can also be used for puncture testing. The bifurcated needle is pressed firmly against the skin, through a drop of extract, and the needle is rocked back and forth or side to side.

A single needle or puncture device can be used for multiple prick skin tests on the same patient, if all residual extract is cleaned from the needle between each drop of extract. Adequate cleaning can usually be accomplished by wiping the needle with an alcohol-soaked pledget or by briefly swirling the device in a container of alcohol. After completing the tests on a patient, the device should be disposed of properly. Tests can be applied to any area of normal skin, but the most commonly used sites are the back, volar forearms, and the top of the thighs. Each test should be placed a minimum of 4 cm or more from other tests, and care should be taken to avoid smearing or mixing of the extracts. Tests placed too close together may run into each other and lead to false-positive reactions.

Intradermal Tests

Intradermal tests are more sensitivite than prick or puncture tests, but they are more difficult to perform properly. Intradermal tests are typically performed with 25-, 26-, or 27-gage needles. Some manufacturers provide needles with a special intradermal bevels, which help limit the depth of needle penetration. After drawing the allergen extract into the syringe, the tip of the needle is inserted into the superficial dermis, and approx 0.02 mL of extract is injected. If the injection is performed properly, a distinct bleb, 2–3 mm in diameter, will be present. Extracts used for intradermal testing are normally diluted 100–1000-fold more than extracts used for epicutaneous tests. As with prick-puncture tests, intradermal tests should be placed at least 4–6 cm apart to prevent interference.

The most common errors with intradermal tests are injecting too deeply, injecting too large a volume, and inducing excess bleeding. If extract is injected too deeply, little or

Type of Allergen Skin Testing in Different Conditions

	Type of skin test	
Condition	*E*[a]	*ID*[b]
Allergic rhinitis and asthma	x	x
Food allergy	x	Not done
Penicillin allergy	x	x
Insect venom allergy	Not done	x (serial)
Latex allergy	Not validated (use in vitro test)	

[a]Epicutaneous: prick, scratch, puncture.
[b]Intradermal.

no reaction will be visible on the surface of the skin. Injecting too large a volume may lead to false-positive reactions because of irritation, and a large volume increases the risk of a systemic reaction. Bleeding at the injection site may also cause false-positive reactions. Because of the risks, technical difficulties, and problems of interpretation, intradermal testing is normally best left to an allergy and immunology specialist.

Positive and Negative Controls for Skin Testing

Because of the many variables present when performing skin testing, positive and negative controls must be included to allow accurate interpretation of test results, regardless of whether the prick, puncture, or intradermal techniques are used. The negative control is either normal saline or the same buffer that has been used to dilute the allergen extracts. The negative control must be applied in the same fashion as all of the other tests.

Positive controls for skin testing are usually either histamine or a mast cell secretagog, such as codeine. For epicutaneous tests, histamine is usually used at a concentration of 1 mg/mL, although some have recommended using a concentration of 10 mg/mL, because a portion of normal individuals do not respond to the 1 mg/mL concentration. For intradermal testing, histamine is most often used at a concentration of 0.01 mg/mL.

Recording and Scoring Skin Test Results

Skin test reactions to allergens are normally evaluated at 15 min after the tests are placed, when the reactions are maximal. Despite many years of use and many investigations, there is still little consensus concerning the scoring and recording of skin test results. The most commonly used system grades both epicutaneous and intradermal tests on a five-point scale, where 0 is a negative test and increasing degrees of reaction are graded from 1+ to 4+, based on the size of both the wheal and flare reactions. In terms of patient management, the actual size or grade of the skin test reaction is less important than the physician's criteria for determining whether the test is positive or negative. Most allergists consider an epicutaneous test positive when the wheal of the test is 2 or 3 mm larger than the wheal produced by the negative control and the wheal is surrounded

by erythema. Similarly, a positive intradermal test should have a wheal at least 5 mm larger than that of the negative control with surrounding flare of 20 mm or more.

Quality Control of Skin Testing

As with all diagnostic tests, persons supervising and performing skin tests should observe certain standards and quality controls. Quality control of skin testing should include making sure that the person performing the tests is knowledgeable, the inter- and intraoperator reproducibility is acceptable, the procedures are consistent, the extract quality is maintained, and the results are consistently recorded. The person performing the tests must know how to apply the tests and factors that may affect the results of the tests, such as interfering drugs and skin abnormalities. Allergen extracts used for testing must be properly stored and discarded when they expire.

Value of Epicutaneous vs Intradermal Skin Tests

Prick tests are adequate from most diagnostic work in allergy, but in some circumstances, the higher sensitivity of intradermal tests is required. This is especially true when dealing with those allergens associated with a high risk of death if the sensitivity is missed, such as with penicillin or hymenoptera allergy. The increased sensitivity of intradermal tests comes at the expense of an increased risk of inducing anaphylaxis, and they are therefore best left to the allergy and immunology specialist.

MEASUREMENT OF ALLERGEN-SPECIFIC IGE

Basic Methodologies

Most available assays for allergen-specific IgE antibodies utilize the principle of immunoabsorption illustrated in Fig. 1. The allergen of interest is first bound to a solid phase support, such as a paper disk or a plastic microtiter well. The patient's serum is then incubated with the solid phase. If the patient has antibodies specific for the allergen, the antibodies will become bound to the allergen, and the remaining serum proteins, including unbound antibodies, can be washed away from the solid phase (this is immunoabsorption and separation). After washing, a labeled antihuman IgE antibody is incubated with the solid phase to allow binding of the anti-IgE to any IgE bound to the solid phase. After washing away unbound anti-IgE, the quantity of anti-IgE bound to the solid phase is measured and converted either to units of specific IgE or to a class score. The initial test for IgE antibodies used radiolabeled anti-IgE antibodies and was called the *r*adio*a*llergo*s*orbent *t*est or RAST. In recent years, other methodologies have become more widely available, leading to a variety of other test eponyms, but all current commercially available assays are based on the immunoabsorption principle. These assays are capable of detecting specific IgE at concentrations of nanograms per milliliter of serum.

Reporting Results of In Vitro Tests

Currently, there is no universally agreed on standard for reporting the results of tests for allergen-specific IgE antibodies. The most commonly used method is class scores, usually ranging from 0 to 4–6. Class 0 indicated undetectable IgE, whereas classes 1–4 or 6 represent increasing quantities of IgE. Some laboratories also report a class 0/1 or

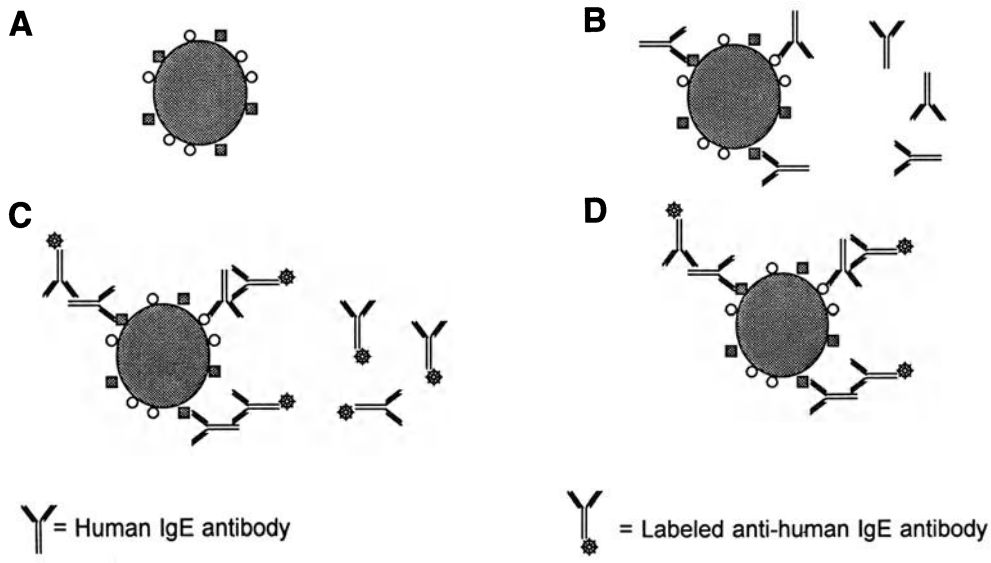

Fig. 1. Schematic presentation of an immunosorbent assay for allergen-specific IgE antibody. (**A**) Allergen represented by small circles and squares has been bound to solid phase. (**B**) Serum that may contain IgE antibodies specific for the allergen is incubated with the solid phase. Specific antibodies bind to the allergen, and nonbound antibodies are removed by washing. (**C**) Labeled antihuman IgE antibody is incubated with the solid phase, and the anti-IgE antibody binds to the immobilized IgE. Nonbound anti-IgE is washed away. (**D**) The amount of anti-IgE antibody on the solid phase is proportional to the concentration of allergen-specific IgE in the serum tested.

indeterminate class. Although some physicians would like to interpret this indeterminate class as a very weak positive, the correct interpretation is that samples in this class have an equal probability of being positive or negative, and should therefore not be considered positive.

To increase the sensitivity of in vitro assays, scoring systems have been modified. The most widely used modified system is known as "modified RAST" scoring. The modified scoring system produces an apparent increase in the sensitivity of the test at the expense of specificity, since only the scoring system and not the actual detection limit of the assay has been changed. Other laboratories score assay results by calculating the ratio of the test serum to the results of sera from known, nonallergic individuals tested in the same assay. Ratios of three or more are usually considered positive.

When interpreting the results of in vitro assays, it is important to remember that the sensitivity and specificity of an in vitro test can vary markedly from one allergen to another. Although in vitro assays typically have sensitivities of 70–80% when compared to skin tests, sensitivities of <50% are found with some allergens.

Advantages and Disadvantages of In Vitro and In Vivo Tests

Depending on the clinical situation, either skin tests or in vitro tests may be used to evaluate a patient for allergen-specific IgE. As listed in Table 2, there are certain advantages of each testing method. The most important advantage of skin testing is the high

Table 2
Comparative Advantages of Skin Tests and In Vitro Tests in Allergy Diagnosis

Advantages of skin tests	*Advantages of in vitro tests*
Highest sensitivity	No risk of anaphylaxis
Results available in minutes	Medications do not affect results
Greater selection of allergens for testing	Not dependent on skin condition
Less personnel and reagent expense per test	Better documentation of quality control
Minimal equipment is required	May be more convenient for patients
Patient can see and feel the results of the test	Perceived as being more scientific

degree of sensitivity. When an intradermal skin test is properly performed, the risk of failing to detect allergic sensitization is extremely low. This degree of sensitivity is very important when the risk of failing to detect specific IgE may lead to the patient's death, as when testing for penicillin allergy.

The most important advantage of in vitro tests is their safety. If an individual has had a life-threatening reaction to an allergen, especially an allergen where there is little prior experience with skin testing or no standardized skin test extract, an in vitro test offers the possibility of detecting specific IgE without subjecting the patient to the risk of an allergic reaction from skin testing. The patient should understand that if the in vitro test is positive and consistent with the patient's history, the diagnosis is relatively assured, but a negative in vitro test does not exclude the possibility of sensitivity. In the face of a suggestive history and a negative in vitro test, the patient should still be skin tested before a final clinical judgment is made.

In routine allergy practice, skin testing has been found to be more cost-effective than in vitro testing. The cost-effectiveness is more pronounced as multiple allergens are tested. There are also the advantages of the patient being able to see the immediate allergic reaction on his or her own skin and the immediate availability of results. In comparison, in vitro tests offer the ability to test patients whose skin is not normally reactive either because of skin disease or because of interfering drugs. It may also be more convenient for both the patient and the physician to send blood samples to reference laboratories for testing, rather than for the patient to travel to another location for the testing.

TOTAL SERUM IGE

Test Methods

Although a variety of assays have been used to measure the small concentrations of IgE normally present in human serum, the most frequently used method is a two site immunometric assay. The first antihuman IgE antibody is attached to a solid phase, such as a paper disk or plastic well in a microtiter plate. The solid phase is first incubated with an appropriate dilution of the serum to be tested. IgE in the serum becomes bound to the solid-phase anti-IgE in proportion to the concentration of IgE in the serum sample. After the nonbound proteins are washed away, the quantity of IgE bound to the solid phase is determined by reacting the solid phase with a second, soluble, labeled anti-IgE

Table 3
Total Serum IgE Levels in Skin Test-Negative Children and Adults

Age, yr	*N*	*Sex*	*Geometric mean*	*Mean ± 2 SD*
6–14	69	M	40.9	2.0–824.1
	71	F	40.7	3.4–452.9
15–34	213	M	23.3	0.9–635.3
	201	F	16.5	0.8–349.1
35–54	145	M	20.4	0.9–443.6
	154	F	14.6	0.7–286.4
55–74	224	M	19.8	0.8–484.2
	348	F	10.7	0.6–198.6
75+	61	M	17.8	0.8–387.3
	83	F	8.9	0.4–208.9

From Klink M, Cline MG, Halonen M, Burrows B. *J Allergy Clin Immunol* 1990; 85:440.

antibody. Following another wash to remove the unbound, labeled anti-IgE, the quantity of labeled IgE is measured and converted into units of IgE by comparison to a standard curve. A variety of commercial assays are available, and most are accurate to a concentration of <5 IU/mL (12 ng/mL) of IgE.

Serum concentrations of IgE vary widely in normal individuals (Table 3). IgE levels are very low at birth and gradually rise, peaking in the second decade of life, followed by a slow decline into old age. Although the geometric mean values are relatively low, there is a very large 95% confidence interval at all ages (Table 3). Most laboratories report IgE concentrations as international units (IU) or nanograms per millilit: 1 IU = 2.4 ng of IgE. The new Système International (SI) specifies that IgE be reported as micrograms per liter (μg/L) with two significant digits ($XX \times 10^n$).

Relationship of Total IgE to Allergic Disease

Most studies have shown that total serum IgE concentrations tend to be higher in allergic adults and children compared to nonallergic individuals of similar ages. Unfortunately, there is a relatively large overlap between serum IgE concentrations in allergic and nonallergic individuals, and this overlap limits the diagnostic value of total IgE measurements. When a high value of IgE is chosen to distinguish allergic from non allergic individuals, the specificity of the test is often over 90% but the sensitivity is low at 30–50%. Lowering the threshold level increases the sensitivity, but lowers the specificity. For adults, the optimal IgE concentration for distinguishing allergic from non allergic individuals varies from 50 to 100 IU/mL, whereas in children the best threshold level varies with age.

Even though measurements of total serum IgE concentrations are not generally useful for diagnosis of allergic disease, total serum IgE measurements are valuable in the diagnosis and management of allergic bronchopulmonary aspergillosis (ABPA). Patients with ABPA typically have serum IgE levels of >500 IU/mL. With adequate glucocorticoid therapy, total serum IgE levels tend to fall. A sudden increase in serum IgE may herald a disease exacerbation and allow time to alter therapy before symptoms increase or more lung damage occurs.

There are other conditions in which total serum levels of IgE may be abnormal. Among the more common nonallergic causes of elevated serum IgE are metazoan parasitic infections, smoking, and AIDS. IgE is grossly elevated in the rare cases of IgE myelomas, which have been reported, but the levels of IgE may still be too low to be detected as a monoclonal spike on serum protein electrophoresis. IgE measurements are important in the evaluation of myelomas, because IgE myelomas may be mistaken for light-chain disease. The distinction between light-chain disease and IgE myeloma is important, because the clinical courses and responses to treatment differ.

THE FUTURE OF ALLERGY TESTING

Currently, most allergy testing concentrates on IgE measurements, but some assays for the direct measurement of mediators are available and more are likely to become clinically relevant. Histamine can be measured during or after allergic reactions, but because it is difficult to collect proper specimens, histamine measurements are usually limited to research studies. Eosinophil cationic protein (ECP) can be measured in sputum or serum, and correlates with the activation of eosinophils. ECP may be useful for monitoring anti-inflammatory asthma therapy. Mast cell tryptase is elevated following massive release of mast cell mediators, such as during anaphylactic reactions. Tryptase levels usually peak 45–60 min after the onset of anaphylaxis and may remain elevated for several hours. Elevated tryptase measurements help document that a reaction resulted from mast cell mediator release. This distinction can be very important in some legal proceedings. For as yet unknown reasons, tryptase does not appear to be elevated during fatal or near-fatal anaphylactic reactions from foods. In the future, assays for histamine-releasing factor and other mediators may make the diagnosis of allergic disease easier and more precise.

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4 Environmental Allergens

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CONTENTS

INTRODUCTION

Allergens are small-mol-wt proteins capable of inducing IgE antibody and triggering an allergic response. In our outdoor and indoor milieu, these allergenic proteins (along with a larger number of nonallergenic proteins) are carried on vectors, such as pollen grains or house dust particles, which may become airborne. Contact with these environmental allergens causes not only the immunologic sensitization required for the development of atopic disease, but also the provocation of acute symptoms and the maintenance of chronic symptoms. Although there are many allergenic proteins on a variety of vectors in the environment, an understanding of a few classes of the major outdoor allergens that cause seasonal symptoms and indoor allergens responsible for perennial symptoms furnishes the physician with practical tools for the care of allergic individuals.

OUTDOOR ALLERGENS

Outdoor allergens are carried most often on plant pollens and mold spores. In order for these particles to be clinically relevant as vectors for allergens, they must reach a high airborne concentration. The level of exposure to these particles is determined by the vicinity of the flora to the patient, the density of production of the pollen or spores by its source, the seasonal and diurnal timing of pollen or spore release, weather conditions, and the aerodynamic characteristics of the vector carrying the allergenic proteins. Flora that are present in great numbers and produce large pollen or spore burdens tend

From: *Allergic Diseases: Diagnosis and Treatment*
Edited by P. Lieberman and J. Anderson Humana Press Inc., Totowa, NJ

Environmental Allergen Exposure

Intermittently, outdoors	Continuously, in the house
• Seasonal plant pollens	• House dust mites
• Mold spores	• Cats, dogs, birds, small animals
	• Mold spores
	• Cockroach

to be the most significant allergenically. Exposure to pollens and mold spores occurs in seasonal patterns that will be detailed in the appropriate sections below.

Airborne concentrations of these particles depend on weather conditions. Pollination and mold sporulation require warmth, and are highest at midday and on warm days. Particle concentration increases with increasing wind speed, but in gusty winds these particles may be swept into the upper atmosphere, reducing ground exposure. In the cool, calm evening hours, these particles may resettle toward the ground, increasing exposure. Surprisingly, the brisk rainfall caused by thunderstorms does not reduce the airborne pollen and spore levels, whereas long periods of rainfall can act to scour these particles and reduce exposure.

The level of exposure to these particles is also dependent on their aerodynamic characteristics. Smaller particles remain airborne for longer periods, increasing exposure levels. Larger particles will settle more quickly, except in high winds. Particle size also determines the manner in which allergen exposure occurs. Particles that are larger than about 10 μm in diameter are deposited largely in the nose and are unlikely to penetrate to the lung. Despite the fact that most mold and pollen spores are 20–60 μm in diameter and impact mostly the eyes and nasal mucosa, patients complain of increased asthma symptoms during the pollen seasons. These particles might induce wheezing through reflexes elicited by nasopharyngeal stimulation, hematogenous spread after the allergenic protein is eluted from vectors at mucosal surfaces, or inhalation of pollen fragments.

Pollen

About 60 families of higher plants in North America are implicated in pollinosis. Pollen contains the male genetic material released from mature anthers. The pollen wall is composed of three layers: an outer exine (composed of external sexine and internal nexine) and an inner intine. The sexine has many micropores, but also larger pores or furrows through which the pollen tube emerges during successful pollination. Allergenic proteins stored in the sexine or intine dissolve through these pores onto mucosal surfaces, allowing hypersensitivity reactions. Many of these proteins have been purified and studied in detail. The major allergens are named with the first three letters of the genus and then the first letter of the species name followed by a group designation, for example Que a 1 (*Quercus alba*—white oak), Amb a 1 (*Ambrosia artemisiifolia*—ragweed), and Lol p 1 (*Lolium perenne*—ryegrass).

The pollen of some plants is dispersed by wind, but other plants disseminate pollen by insect or animal vectors. Wind-dispersed (anemophilous) pollens achieve high airborne concentrations and are primarily responsible for clinical allergy. These anemophilous plants tend to have small, nonaromatic flowers, little or no nectar, and

Plant Pollens

- The type of pollens responsible for seasonal allergies tend to be small, light, and windblown. They are dispersed in large numbers from plants that have small, nondiscrete flowers.
- The specific "pollinating seasons" for different tree, grass, or weed plant species vary within different areas of the country.
- Airborne concentration of pollens depends on the weather. Levels tend to be highest at midday during warm, slightly windy conditions.

produce large numbers of pollen grains that have aerodynamic properties to improve buoyancy. The majority of flowering plants, however, rely on animal or insect vectors for pollination (entomophilous) and these species—with their large, aromatic, colorful flowers—are not clinically relevant because their pollens are not airborne.

The published pollen counts can be a very helpful guide for understanding what is "in season." Pollens are collected in a standardized fashion using machines that trap the pollen either actively with rotating arms coated with adhesive substances or by passive wind and gravitational force. The pollen grains from various species have distinct morphologies and, after collection, can be identified under the light microscope. However, the interpretation of these counts and their relevance to the individual patient must be considered. For example, daily variation may be extreme, making interpretation for daily symptom predictions difficult. In addition, symptom intensity depends on many factors, so reporting of a doubling in pollen count, for example, may not be clinically relevant to an individual whose threshold level of allergen that causes symptoms has not been reached. In any event, knowing the patient's particular sensitivities, the yearly timing of his or her symptoms, the seasonal timing of pollination, and the characteristics of local fauna will help to guide patient care.

Pollen Seasons

In temperate regions, pollen seasons are traditionally grouped as trees, grasses, and weeds: Trees pollinate from late winter to late spring, grasses from late spring to midsummer, and weeds from midsummer to autumn. However, this delineation may vary widely depending on the yearly weather pattern and geographic location. Figure 1 shows the timing of pollination of allergenically significant trees, grasses, and weeds by region in North America.

Tree Pollen

Tree pollination heralds the beginning of the allergy season in most climates in North America and begins in late February through April, although the season may begin as early as December or January in areas of Arkansas, south Florida, and Texas. In general, the greatest variety and concentration of tree pollens occur in March through May with the season ending in June. Some examples of species that pollinate earlier in the tree season include red cedar and elm. Midseason pollinating species include poplar, birch, ash, and willow, with late-season pollination by sycamore, oak, and mulberry. Table 1 shows five allergenically significant trees in each region of North America shown in the sequence in which they bloom. Trees on this list were selected to illustrate both signifi-

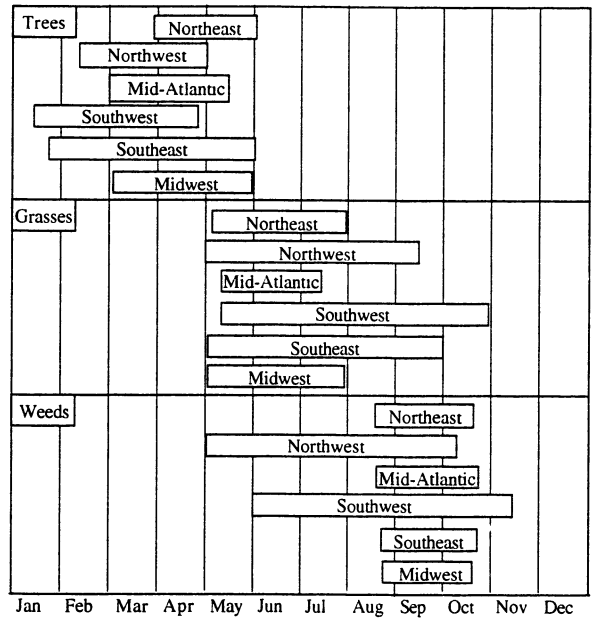

Fig. 1. Pollen seasons by region in the continental United States.

cant species and the breadth of pollens that contribute to the span of the tree season in each area.

Grass Pollen

In most areas of North America, the grass pollen season overlaps and follows the close of the tree pollen season. It extends from May through July, although there is much variation. Prominent grasses in temperate regions include orchard, timothy, ryegrass, and bluegrass. Each grass pollen contains distinct allergenic proteins, but there is significant allergenic crossreactivity among the proteins, and patients are generally sensitized to all of these pollens. Because of this crossallergenicity, differences in exposure to specific temperate grass species are not clinically significant, as they are for tree or weed pollens. In the southern states and subtropical regions, Bermuda, Bahia, and Johnson grasses play a larger role in pollinosis. The allergens in these southern grass pollens are distinct. In some subtropical areas Bermuda grass and other species may produce almost perennial pollination. Table 1 shows examples of allergenically significant grasses by region in North America.

Weed Pollen

Weed pollination typically occurs in the late summer through October in most regions of North America. There are a tremendous variety of weeds, but ragweed species (*Ambrosia*) are responsible for the greatest amount of seasonal symptoms in the fall. Ragweed typically begins pollinating in mid-August and stops in October. All species contain the major allergen Amb a 1, so sensitized individuals may experience symptoms "out of season" when visiting regions where different species pollinate perennially, such as Coastal ragweed, which is prevalent in winter months in southern Florida. In addition to ragweed, other weeds are responsible for significant regional allergy, in-

Table 1
Selected Trees and Weeds of Allergenic Significance[a]

Region	*Trees*	*Grasses*	*Weeds*
Northeast	Birch	Orchard	Sheep sorrel
(ME, NH, VT, NY, PA,	Elm	Timothy	Plantain
NJ, MA, RI, CT)	Maple	June	Russian thistle
	Poplar	Sweet vernal	Giant ragweed
	Oak	Bluegrass	Short ragweed
Mid-Atlantic	Birch	Orchard	Plantain
(DE, MC, DC, VA, NC, SC)	Elm	Timothy	Dock
	Maple	Bluegrass	Sage
	Hickory	June	Short ragweed
	Oak	Bermuda	Giant ragweed
North Central	Ash	Orchard	Plantain
(OH, KY, WI, MI, IA, WI,	Elm	Timothy	Dock
northern MO, IL, IN, TN)	Maple	Bluegrass	Russian thistle
	Willow	June	Short ragweed
	Box Elder		Giant ragweed
Pacific Northwest	Alder	Timothy	Dock
(WA, NV, OR, northern CA)	Birch	Bluegrass	Plantain
	Maple	Fescue	Russian thistle
	Oak	Rye	Nettle
	Walnut	Redtop	Sagebrush
Plains	Elm	Timothy	Marsh-elder
(NE, MN, eastern MT, Dakotas)	Oak	Orchard	Russian thistle
	Box Elder	Bluegrass	Western hemp
	Willow	Bermuda	Short ragweed
	Maple	Redtop	Giant ragweed
Rocky Mountains	Cedar	Timothy	Sagebrush
(ID, WY, CO, UT, western MT)	Elm	Orchard	Russian thistle
	Ash	Fescue	Short ragweed
	Birch	Redtop	Giant ragweed
	Oak	June	
Southern	Cedar	Bermuda	Dock
(FL, GA, AL, TX, AR, southern MO)	Elm	Orchard	Pigweed
	Mulberry	Timothy	Russian thistle
	Poplar	Saltgrass	Giant ragweed
	Oak		Short ragweed
Southwest	Cedar	Bermuda	Sagebrush
(western TX, NM, AZ)	Ash	Johnson	Russian thistle
	Mulberry		Saltbush
	Oak		Kochia
	Olive		Short ragweed
Southern California	Ash	Bermuda	Nettle
	Walnut	Saltgrass	Bur ragweed
	Elm	Brome	Russian thistle
	Oak		Sage
	Olive		Western ragweed

[a]Plants are shown in the order of bloom for each region. Grasses are listed by prevalence in each region.

cluding pigweed, amaranth, marsh elder, dock, sorrel, plantain, and Russian thistle, among others. Allergenically significant weeds are listed by region in the order of bloom within the weed pollen season in Table 1.

Fungi

Fungal spores (the term "molds" refers to fungi that lack macroscopic reproductive structures, but may produce visible colonies) are responsible for both seasonal and perennial allergic symptoms, and there are both indoor and outdoor varieties. Despite being able to survive a variety of extremes in temperature and humidity, most fungal forms grow best on a moist substrate. Outdoor varieties include *Cladosporium, Alternaria, Aspergillus, Penicillium*, and *Botrytis*. Allergenic proteins are found in the spores and in other fungal elements that may become airborne. Many of the allergenic proteins produced by these fungi have been characterized at the molecular level, such as Alt a 1 (*Alternaria alternata*) and Cla h 2 (*Cladosporium herbarium*).

In general, temperate grasslands are a strong source of *Alternaria, Cladosporium, Helminthosporium-Drechslera*, and *Epicoccum* species. Outdoor fungal particle levels peak in the midsummer in most temperate regions, but large daily variations are superimposed on this trend. Typical midwestern seasons of *Alternaria* and *Cladosporium* occur in late summer. Fungal spore exposure may also increase in the spring, when snow uncovers decaying vegetation, and the period after rains may also increase the prevalence of mold spores. Patients' symptoms that occur during outdoor activities that stir vegetation, such as leaf raking, farming activities, grass cutting, or hiking, are generally attributable to fungus exposure. Although grass pollen, insect debris, and other allergens can be stirred by these activities, the role of fungal allergens should not be overlooked.

INDOOR ALLERGENS

The house dust found in the indoor environment is a complex mixture that includes various levels of the outdoor particles mentioned above, dust mite particles, fungal spores, animal dander, bacteria, food remnants, and a variety of inorganic materials. Many atopic individuals experience perennial symptoms because of allergens in the indoor environment. Frequently, even perennial symptoms may wax and wane, making physician detective work and diligent history taking imperative. For example, a dog-allergic patient may experience an increase in symptoms during the winter months when an outdoor pet spends more time indoors.

Just as it is possible to count pollens by morphological characteristics, the measurement of indoor allergen concentrations is also possible, but requires different methods. Determining the concentration of these indoor allergens is often helpful clinically, since exposure levels are less predictable than seasonal outdoor allergens. Molds may be measured by colony counts and dust mites can be counted in measured dust samples using a light microscope. Monoclonal antibody (MAb) assays to major allergens of dust mites, cat, dog, and cockroach among others have made analysis of exposure levels to a number of relevant allergens possible. This work provides data to support the notion that there is a threshold level of a particular allergen that predisposes susceptible individuals to become sensitized, and that there is a higher threshold level above which symptoms may be elicited. Thus, steps taken to reduce levels of relevant indoor aller-

Mold Spores

- Mold growth requires moisture.
- Mold spores can be found in the air year-round, but tend to peak in the spring, late summer, and fall with wet weather.
- Mold growth can also be a problem in the house, especially in the basement, bathrooms, and other areas that are damp.

gens may help to prevent the development of specific allergic sensitization as well as reduction of symptoms. This work has also helped to elucidate the aerobiologic properties of these allergens and the steps needed to reduce exposure to them.

Dust Mites

The most important allergen in house dust derives from house dust mites. The almost ubiquitous domestic house dust mites, the most prominent of which are *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, are in the same family as scabies. They are microscopic (approximate 0.3 mm in length), eight-legged, and feed on human skin scales. They rely on ambient humidity for water, which they absorb through a hygroscopic substance on their legs. They grow best at a relative humidity in excess of 75%, which may be easily achieved in, for example, a mattress, even when ambient humidity is lower. This requirement for humidity also results in a lower concentration of mites in surface dust as opposed to deeper areas such as in blankets, pillows, and furred toys. The number of dust mites in the environment will correlate with absolute humidity, which can lead to seasonal variation in exposure levels. The optimal temperature for their growth is 18.3–26.7°C. These requirements for growth explain why they are not as prevalent an allergen in cold, dry areas, such as northern Sweden, central Canada, and at high altitudes as in Colorado.

The major source of mite allergen is derived from fecal particles that are 10–35 μm in diameter (similar to the size of pollen grains). The fecal particles can become airborne with disturbance, but settle rapidly. The particles are surrounded by a membrane that allows contained allergen to elute when in contact with wet surfaces, such as mucous membranes. Although a patient may give a history that is suggestive of dust mite allergy, such as acute symptoms occurring on going to bed, frequently the role of this allergen may be more in the realm of chronic inflammation and chronic symptoms.

Fungi

Examples of common indoor fungi include *Penicillium, Aspergillus, Rhizopus*, and *Cladosporium*. Fungal colonies may be visible as darkly stained growths or may be detected by a "musty" odor in some cases. *Penicillium*, for example, forms the greenish growth in damp areas, and *Rhizopus* is the fluffy black growth seen on old bread. Damp basements, soiled upholstery, garbage containers, various wet bathroom items, and damp food or clothing storage areas are excellent sources for mold growth. Humidifiers that use a cold water reservoir and duct systems that have become damp may also disperse fungal allergens. Since molds are ubiquitous, trying to culture them from a patient's home environment may not be as helpful as correlating symptoms, exposure risks, and skin test or RAST results in diagnosing their role in an individual's symp-

toms. Like pollens, outdoor airborne fungal allergens can become a significant indoor allergen by virtue of entry through doors and windows.

Animal Danders

An estimated 100 million domestic animals reside in the United States, with from one-third to one-half of homes having a pet, the most popular being cats and dogs. Animal dander carrying the allergenic proteins derive from emanations that include skin scales, urine, feces, and saliva. Exposure to a pet may elicit acute symptoms, but more often animal allergen in the home is responsible for chronic symptoms, often making the suspicion of an allergy to a household pet more difficult to diagnose. Finally, it must be remembered that pets may act as a vector for bringing outdoor allergens, such as pollen, into the home environment.

Cats

Cats are among the most common household pet in urban areas, and survey data would indicate that 20–40% of the atopic population is sensitized to cat allergen and about one-third of these people live with cats. The major allergen responsible for cat allergy is Fel d 1, although reactivity to other proteins, including cat albumin, play a role. All breeds, both long and short hair, produce Fel d 1 to varying extents, and males produce more than females. Even "big cats" (e.g., tigers) produce this allergen. The allergen is found in both saliva and sebaceous glands, and is distributed by licking and grooming. The size of vectors that carry the allergen are generally <25 μm, and 10–30% are smaller than 2.5 μm. These small particles remain airborne for long periods of time and are not readily cleared by the nasopharynx. This ability of the particles to reach the lower airway may explain the sudden asthma symptoms some sensitive individuals experience on entering a home with cats. Cat allergen has been found in low levels even in homes without cats or in schools; presumably, the allergen is brought in by passive transport from cat owners, since these particles are adherent. In fact, cat allergen is tenacious, in that it has been detected not only in settled dust, but also on walls and fabrics and can remain for months after a cat is removed from the home.

Dogs

The prevalence of sensitivity to dog allergen is about half that seen with cat sensitivity. The major dog allergen is Can f 1, which is detected on the coat and in saliva. The amount produced by different breeds varies, but all breeds produce the major allergen so there is not truly an allergen-free breed. Some breeds do, however, produce breed-specific allergens, but the clinical relevance of this is not well understood. The airborne characteristics of dog allergen are not well described. Like cat allergen, the dog major allergen can be detected in homes without dogs or in schools, showing that passive transport and persistence of allergen is possible.

Birds

IgE-mediated sensitivity to feathers has been found in canary fanciers and other bird breeders, but the prevalence of sensitization is not known. Positive skin tests to feather extract may be related to contamination of the extract with mite allergen, leading to false estimates of the prevalence of sensitivity. Similarly, feather pillows may induce symptoms because of the growth of house dust mites or mold in them, rather than any

avian proteins associated with the feathers. Specific disease caused by bird exposure is, however, seen in pigeon breeders and budgerigar, canary, and other bird fanciers who may develop hypersensitivity pneumonitis. IgG antibody responses toward the avian serum gamma globulin is seen in these patients, although IgE-mediated sensitivity has also been demonstrated in some individuals with this disease.

Other Furred Animals

Furred animals other than cats and dogs are found in homes, schools, farms, and the workplace. Furred pets found in homes or schools include hamsters, gerbils, guinea pigs, rabbits, and many exotic pets. The allergens from these animals may be found in their fur, urine, and saliva. Farm animals, such as pigs, cattle, and horses, are also responsible for allergic disease, although little is known about the prevalence of disease activity from these sources in the United States. Sensitivity to these farm animals is a more common problem in northern Europe, presumably because of the closer proximity of these animals to the homes of their keepers.

Furred pests, such as mice and rats, should also be considered as a potential source of allergen. Mouse allergen (Mus m 1) has also been detected in air samples from urban dwellings, but the role in atopic disease in that setting is not well characterized. Among laboratory workers exposed to animals, 11–30% show sensitivity, and most of these individuals become sensitive to more than one species. Studies with laboratory workers handling rats have shown that rat allergen (Rat n 1) levels vary widely depending on the type of disturbance—cleaning cages, sacrificing—the animals are undergoing, which may play a role in sensitization and the production of symptoms.

Insects

The fine wing scales, fecal pellets, and other emanations from moths, locusts, various beetles, flies, and other insects are a source of inhalant allergens. The mayfly, for example, is responsible for allergic symptoms especially in the area around the western end of Lake Erie. The allergen from the mayfly is carried on particles that are fragments of the insect's pellicle shed during molting.

Among the various insects that have been implicated in allergy, the cockroach is the best studied. Three main species of cockroach inhabit buildings: *Blattella germanica, Periplaneta americana*, and *Blatella orientalis; B. germanica* is the most prevalent in crowded cities. Its major allergens, Bla g 1 and Bla g 2, derive principally from the saliva and fecal material. The larger American cockroach produces the allergen Per a 1, which crossreacts with Bla g 1. Sensitivity to cockroach allergen has been shown to be associated with a history of infestation, is more prevalent in urban as compared to suburban areas, and has been associated as a risk factor for emergency room visits for asthma in the inner city. Although concentrated in kitchen and bathrooms, allergen is detectable in all areas of the home.

Other Indoor Allergens

There are a number of other potential allergens that are detectable in the indoor environment, but their role in disease is not well understood. These include indoor plant material, bacteria, protozoa, algae, food debris, and low-mol-wt chemicals. Indoor plants do not usually produce pollen, but some may be allergenic, such as the airborne leaf par-

ticles of *Ficus benjamina* (weeping fig). Other plant materials, such as latex and dust from cotton, coffee, and flour, are probably only relevant in the industrial setting. Products such as enzymes secreted from bacteria and protozoa have been implicated in allergic disease, but the exact pathophysiology or epidemiology is not completely understood. Food allergens, such as ovalbumin, become aerosolized in certain industrial conditions and may provoke allergic reactions as well.

Low-mol-wt chemicals, such as anhydrides, isocyanates, azo-dyes, and ethylenediamide, have been reported to cause allergic reactions in industrial settings. These chemicals are too small to evoke immune reactions unless they complex with proteins. Most exposures occur in industrial settings and not in domestic settings, unless acrylic paints or glues are used without ventilation. Some of these chemicals may act as irritants rather than allergens. Again, the exposure history is important in considering these agents, and their significance in nonindustrial settings is unclear.

ACKNOWLEDGMENTS

This work was supported in part by the Hospital for Consumptives of Maryland (Eudowood Fund) and The Harriet Lane Research Fellowship.

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5 Anaphylaxis

Phil Lieberman, MD

CONTENTS

INTRODUCTION

The term, "anaphylaxis" refers to a systemic, immediate hypersensitivity reaction resulting from IgE-mediated mast cell and/or basophil degranulation. This degranulation releases chemicals responsible for the clinical event. The term, "anaphylactoid reaction" refers to a clinically similar occurrence not mediated by IgE.

ETIOLOGY AND PATHOPHYSIOLOGY

Anaphylaxis and anaphylactic events can be classified etiologically and pathophysiologically, as seen in Table 1. The most common causes of true, IgE-mediated anaphylaxis are drugs, foods, insect bites and stings, and latex. Antibiotics are probably the most common cause of drug-induced anaphylaxis. Penicillin and its derivatives are the most common antibiotics to cause anaphylactic reactions.

The exact incidence of anaphylaxis to foods is unknown. However, anaphylaxis to foods and drugs are the most common reported causes. The most common offender in adults is probably shellfish and in children probably peanuts. Foods can cause anaphylactic fatalities. Insect bites and stings cause several deaths in the United States each year. The incidence of latex-induced anaphylaxis has increased dramatically over the last decades with the increased use of latex gloves.

Non-IgE-mediated, anaphylactoid episodes can occur via several different mechanisms. Aspirin and other nonsteroidal anti-inflammatory drugs are important causes of anaphylactoid events. They apparently produce anaphylactoid reactions through the aberrant metabolism of arachidonic acid. However, some episodes may be caused by the direct degranulation of mast cells.

From: *Allergic Diseases: Diagnosis and Treatment*
Edited by P. Lieberman and J. Anderson Humana Press Inc., Totowa, NJ

Table 1
Etiologic and Pathophysiologic Classification of Anaphylaxis and Anaphylactoid Reactions

Anaphylaxis—IgE-mediated reaction
Drugs
Food
Insect bites and stings
Latex
Perhaps some cases of exercise
Anaphylactoid
Disturbances in arachidonic acid metabolism
Aspirin
Nonsteroidal anti-inflammatory drugs
Immune aggregates
γ Globulin
IgG-anti-IgA
Possibly protamine, dextran, and albumin
Direct release of mediators from mast cells and basophils
Drugs
Idiopathic
Exercise
Physical factors, such as cold or sunlight
Miscellaneous and multimediator activity
Nonantigen–antibody-mediated complement activation
Radiocontrast material
Possibly some cases of protamine reactions
Dialysis membranes
Activation of contact system
Dialysis membranes
Radiocontrast material

Antigen–antibody aggregates (immune aggregates) cause anaphylactoid reactions by activation of the complement system. Intramuscular γ globulin, protamine, dextran, albumin, and transfusions in IgA-deficient patients have all been incriminated as causes of this form of anaphylactoid reaction.

Some drugs produce anaphylactoid reactions by directly degranulating mast cells and basophils. That is, they do not act through IgE, but through a putative receptor on the mast cell and basophil surface. Several drugs, including radiocontrast media and opioids, can cause anaphylaxis via this mechanism. In addition, some patients with idiopathic anaphylaxis, exercise anaphylaxis, and anaphylaxis owing to physical factors, such as cold and sunlight, may experience their episodes through direct mast cell and basophil degranulation.

Many agents are capable of activating complement and the contact system (kallikrein and kinins). These include radiocontrast material, dialysis membranes, and possibly protamine. It is likely that the majority of anaphylactic episodes do involve mast cells and basophils. Therefore, an understanding of the pathophysiology of the event is dependent on a knowledge of the contents of these cells. These contents and their role in the production of anaphylaxis and anaphylactoid events are seen in Table 2. Histamine

Pathophysiology

- Histamine, through its action on both H_1 and H_2 receptors, is probably the major mediator of most episodes of anaphylaxis.
- The contents of mast cells and basophils can activate other biochemical pathways, such as clotting, clot lysis, complement, and the contact (kinin) system, all of which can contribute to the event.
- Protracted and recurrent symptoms can occur and are probably owing to chemotaxis of inflammatory cells.

is certainly a major mediator, and histamine infusion has been shown to reproduce the majority of the manifestations of anaphylaxis. Therefore, its activities are reviewed in more detail in Table 3. The actions of histamine are mediated through three receptor types (H_1, H_2, and H_3). Two of these, the H_1 and H_2 receptors, are active in producing the symptoms of anaphylaxis.

The overall effect of histamine on the vascular bed is to produce vasodilatation. This causes flushing and a lowering of peripheral resistance, resulting in a fall in systolic pressure. Vascular permeability also occurs, owing to a separation of endothelial cells at the postcapillary venule level. Both H_1 and H_2 receptors are operative in the production of vasodilatation. Part of this effect is the result of the production of nitric oxide, a potent vasodilator, by endothelial cells stimulated through their H_1 receptors.

Cardiac effects of histamine are mediated primarily through the H_2 receptor. H_2 receptor stimulation causes an increase in rate and force of atrial and ventricular contraction, and decreases the fibrillation threshold. H_1 receptor stimulation can cause coronary artery vasospasm and an increased rate of depolarization of the SA node. Histamine vasoconstricts smooth muscle in the bronchial tree, uterus, and gastrointestinal tract. Glandular secretion is increased by both H_1 and H_2 stimulation.

The role of other basophil and mast cell mediators has not been as clearly defined. However, arachidonic acid metabolites, such as the leukotrienes (LTC4, D4, E4) and the prostaglandins (PGD_2, PGF_2-α), as well as thromboxane A_2 can cause contraction of airway smooth muscle, increased vascular permeability, goblet and mucosal gland secretion, and peripheral vasodilatation. Platelet activating factor also contracts smooth muscle and enhances vascular permeability.

Thus histamine, arachidonic metabolites, and platelet activating factor produce smooth muscle spasm, enhance vascular permeability, cause vasodilatation, stimulate sensory nerves thus activating vagal effector pathways, and alter myocardial function. The results of these events are the classical symptoms of flush, urticaria and angioedema, wheeze, hypotension and shock, myocardial ischemia, and gastrointestinal smooth muscle contraction with nausea, vomiting, and diarrhea.

Other mediators, such as tryptase, chymase, mast cell kininogen, and basophil kallikrein, can recruit secondary inflammatory pathways. These secondary inflammatory pathways include the coagulation pathway, the complement cascade, the contact system (kinin formation), and the synthesis of neuropeptides (Table 4). Tryptase can activate complement by cleaving C_3 to C_3a. Tryptase also cleaves fibrinogen and perhaps has kallikrein activity, thus causing the formation of kinins. Both mast cells and basophils contain substances that result in kinin formation. Chymase can induce the syn-

Table 2
Mast Cell and Basophil Mediators That May Play a Role in Anaphylaxis and Anaphylactoid Reactions

Mediator	*Pathophysiologic event*	*Possible clinical manifestations*
Histamine	Acts through H_1, H_2 receptors Contraction of smooth muscle Vasodilatation Increased vascular permeability Exocrine gland secretion Irritation sensory nerves	Flush, urticaria, angioedema, wheeze, hypotension, abdominal cramps, diarrhea
Arachidonic acid metabolites		
• Lipoxygenase pathway		
LTB4	Chemotaxis	Possible role in late-phase response
LTC4	Contraction airway smooth muscle	
LTD4	Increased vascular permeability	Possible production of wheeze and hypotension
LTE4	Goblet and mucosal gland secretion	
• Cyclooxygenase pathway		
PGD_2	Peripheral vasodilatation	Flush, hypotension
$PGF_2\ \alpha$	Contraction airway smooth muscle	Possible production of wheeze, myocardial ischemia
Thromboxane A_2	Coronary vasoconstriction Goblet, submucosal gland secretion	
Platelet activating factor	Contraction airway smooth muscle Vascular permeability	Wheeze, hypotension
Eosinophil and neutrophil chemotactic factors	Infiltration of and activation of eosinophils and neutrophils	Unclear—theoretically could prolong and intensify reaction, producing late-phase reaction
Mast-cell kininogenase and basophil kallikrein	Activate contact system with formation kinins	Unclear
Tryptase	May activate complement by cleavage C3 to $C3_a$ Cleaves fibrinogen Possibly has kallikrein activity	Unclear—may recruit other pathways of inflammation
Chymase	Cleaves neuropeptides Converts angiotensin I to angiotensin II	May play role in response to hypotension with conversion of angiotensin—could have salutary effect by inactivation of neuropeptides
Heparin	Inhibits clotting, plasmin, and kallikrein; also anticomplementary	May have salutary (anti-inflammatory) effect

thesis of neuropeptides, including substance P and vasoactive intestinal polypeptide. These secondary pathways can play a profound role in severe anaphylactic episodes. Patients in anaphylactic shock have been shown to have decreased Factor V, Factor

Table 3
Actions of Histamine Pertinent to Anaphylaxis Mediated Through H_1 and H_2 Receptors

H_1	*H_2*	*Requires H_1 and H_2 for maximum effect*
Smooth muscle contraction	Cardiac effects	Vasodilatation
Vascular permeability	Positive chronotropic	Hypotension
Stimulation of nerve endings	Positive inotropic	Headache
Pruritus	Decreased fibrillation threshold	Flush
Vagal irritant receptors		
Neuropeptide release	Vasodilatation	Increased amount mucous gland secretion
Vasodilatation	Mucous glycoprotein secretion from goblet cells and bronchial glands	
Endothelial cell-relaxing factor (nitric oxide)		
Direct effect		
Cardiac effects		
Increased rate of depolarization of SA node		
Coronary artery vasospasm		
Increased viscosity mucous gland secretion		

Table 4
Multimediator Recruitment Occurring During Anaphylaxis and Anaphylactoid Events

Coagulation pathway
Decreased Factor V
Decreased Factor VIII
Decreased fibrinogen
Complement cascade
Decreased C_4
Decreased C_3
Formation $C3_a$
Contact system (kinin formation)
Decreased high-mol-wt kininogen
Formation of kallikrein-C_1-inhibitor complexes, factor XIIa-C_1-inhibitor complexes
Neuropeptides
Substance P
Vasoactive intestinal polypeptide

VIII, fibrinogen, C_4, C_3, and formation of C_3a. In addition, there is evidence for kinin formation and the synthesis of neuropeptides.

It is also important to note that chemotactic factors are released from mast cells and basophils. These factors recruit other cells, which then degranulate and release a second wave of mediators. This second wave of mediators is thought to account for relapses of

Clinical Manifestations

- The vast majority of patients will demonstrate cutaneous manifestations (flush, urticaria).
- Hypotension can occur in patients maximally vasoconstricted because of endogenous catecholamines and angiotensin; the hypotension in these cases is the result of a depressed intravascular volume.
- In most instances, the earlier the onset of symptoms after exposure to the responsible agent, the more severe the episode.

anaphylaxis that can occur after initial symptoms have resolved. These are termed "late-phase reactions." In addition, these chemotactic events along with the recruitment of other mediators can result in protracted or prolonged episodes of anaphylaxis that persist long after the initial degranulation of mast cells and basophils.

Signs and Symptoms

The signs and symptoms of anaphylaxis as obtained from a review of several series, in order of frequency, are seen in Table 5. Clearly, the most common organ involved is the skin. Urticaria and angioedema are the most common cutaneous manifestations, occurring in approx 88% of patients. Flush occurs in approx 46% of patients, and a small percentage of patients can have pruritus without rash. Anaphylaxis and anaphylactoid events can occur in the absence of cutaneous symptoms, but this is relatively rare.

Respiratory symptoms are the next most common. Shortness of breath and wheeze are present in approx 48% of subjects. Upper airway edema causing shortness of breath is present in approx 56% of patients.

Symptoms of hypotension and documented hypotension appear next most frequently and are noted in approx 33% of patients. It is important to understand the mechanism of production of shock in anaphylaxis. Initially the major factor causing shock is a loss of intravascular volume accompanied by vasodilatation. Shortly thereafter, there can be myocardial depression. However, it should be noted that vasoconstriction, owing to compensatory mechanisms, can occur. Therefore, patients with profound shock can be maximally vasoconstricted. In these patients, vasopressors may be of little value, and fluid administration is the most effective form of therapy. The compensatory mechanisms resulting in vasoconstriction are the conversion of angiotensin I to angiotensin II and the endogenous synthesis of catecholamines (norepinephrine and epinephrine).

The gastrointestinal tract is the next most common system involved. Symptoms include nausea, vomiting, diarrhea, and cramping abdominal pain. Less frequent symptoms are headache, rhinitis, substernal pain, and seizure (presumably secondary to hypotension).

It should be noted that cardiovascular collapse with shock can occur immediately without cutaneous or respiratory symptoms. Manifestations usually begin within 5–30 min after antigen has been injected. However, there can be a delay of an hour or more. Oral administration usually produces symptoms within the first 2 h of ingestion, but symptoms can be delayed in onset for several hours. It is thought that there is a direct correlation between the immediacy of onset of symptoms and the severity of a given attack. The more rapid the onset, the more severe the episode.

Table 5
Frequency of Occurrence of Signs and Symptoms of Anaphylaxis[a]

Signs/symptoms	*Approximate percent of patients experiencing*
Urticaria and angioedema	88
Dyspnea, wheeze	47
Dizziness, syncope, hypotension	33
Nausea, vomiting, diarrhea, cramping abdominal pain	30
Flush[b]	46
Upper airway edema[b]	56
Headache[b]	15
Rhinitis[b]	16
Substernal pain[b]	6
Itch without rash[b]	4.5
Seizure[b]	1.5

[a]Based on a compilation of the following references: (1) Kemp S, Lieberman P, Wolf B. A review of 267 cases of anaphylaxis in clinical practice. *J Allergy Clin Immunol* 1993; 91: 153 (abstract-supplement). (2) Wade JP, Liang MH, Sheffer AL. Exercise-induced anaphylaxis: epidemiological observations. *Prog Clin Biol Res* 1989; 297: 175. (3) Wiggins CA. Characteristics and etiology of 30 patients with anaphylaxis. *Immun Allergy Pract* 1991; 13(8): 313–316. (4) Orfan NA, Stoloff RS, Harris KE, Patterson R. Idiopathic anaphylaxis: total experience with 225 patients. *Allergy Proc* 1992; 13(1): 35–43.

[b]Symptom or sign not reported in all four series.

As noted, an episode can abate and then recur several hours after symptoms have disappeared. Thus, the anaphylactoid event can occur in a biphasic form. Also, there can be protracted anaphylaxis with symptoms persisting without interruption over 24 h. This is especially true for cardiovascular manifestations. Both biphasic anaphylaxis and protracted anaphylaxis can occur in spite of appropriate therapy. Death can occur at any time during the course of protracted anaphylaxis.

The cardiac manifestations of anaphylaxis can be varied and profound. Usually there is a compensatory tachycardia resulting from a decreased effective vascular volume. This has often been used as a sign to differentiate anaphylaxis from vasodepressor reactions. However, bradycardia, presumably owing to increased vagal tone, can also occur during anaphylaxis. This is thought to be owing an activation of the Bezold-Jarisch reflex. This cardio-inhibitory reflex is transported by unmyelinated vagal C-fibers and is the result of ischemic stimulation of sensory receptors in the inferoposterior wall of the left ventricle.

Myocardial depression with a significant decrease in cardiac output can occur and can last several days. This is presumably the result of hypoxemia and the direct effect of mediators released from mast cells and basophils. Coronary artery vasospasm with myocardial infarction can occur. Electrocardiographic abnormalities are common, and include flattening or inversion of T waves, ST segment elevation, and arrhythmias. Cardiac enzymes can be elevated during these episodes.

Arterial gas abnormalities usually consist of a fall in PO_2 and PCO_2 early in the course. If severe respiratory difficulties supervene, hypoxemia worsens, and an elevation of PCO_2 and fall in pH can also occur.

Death from anaphylaxis is usually the result of respiratory obstruction and/or cardiovascular collapse. In patients dying from respiratory obstruction, there is edema of the

airway and pulmonary hyperinflation. Upper airway edema occurs in over 50% of deaths. Bronchial obstruction with hyperinflation occurs in approx 50%. The obstruction is the result of a combination of submucosal edema, bronchial spasm, and secretions.

In some instances, death occurs without any gross pathologic change and is presumably the result of sudden and profound cardiovascular collapse. In such cases, myocardial damage can usually be detected microscopically.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of anaphylaxis and anaphylactoid events is seen in Table 6. This classification includes events that need to be considered when the patient is seen not only during the acute episode, but afterward for the purpose of determining the cause of the event. Anaphylaxis, as noted, occurs not only to exogenous agents, but also after exercise, exposure to certain physical factors, and in many instances without known cause.

Perhaps the most common condition mimicking anaphylaxis is the vasodepressor reaction. Such reactions are characterized by hypotension, weakness, nausea and vomiting, pallor, and sweating. They are usually caused by a threatening event or emotional trauma. Bradycardia rather than tachycardia is a characteristic feature of vasodepressor reactions. This can be used as a differential diagnostic factor to distinguish a vasodepressor reaction from an anaphylactic event. However, as noted, bradycardia can also occur in anaphylaxis. Another important distinguishing feature is the absence of cutaneous manifestations (flush, urticaria, angioedema, or pruritus). There are several conditions that produce flush that can be confused with anaphylaxis. These include the carcinoid syndrome, postmenopausal flush, chlorpropamide-alcohol-induced flush, flush associated with medullary carcinoma of the thyroid, and autonomic epilepsy.

Carcinoid tumors can secrete histamine, neuropeptides, kallikrein, and prostaglandins in addition to 5-hydroxytryptamine (serotonin). It is therefore not surprising that they cause symptoms and signs similar to those that occur during anaphylactic episodes. Patients with carcinoid syndrome have flushing, abdominal pain, diarrhea, and occasionally wheezing. Postmenopausal flush occurs over the face, neck, breasts, and upper chest. The flush can last 3–5 min and occurs several times a day. It is aggravated by stress and alcohol. There is no hypotension.

The ingestion of alcohol with a sulfonylurea agent, especially chlorpropamide, causes a flush associated with hypoglycemia and all of its attendant symptoms. The flush usually begins 3–5 min after alcohol ingestion and peaks in about 15 min. There is no hypotension, syncope, or gastrointestinal symptoms.

A protracted flush can occur with medullary carcinoma of the thyroid. It appears over the face and upper extremities. Patients usually have telangiectasia and a positive family history of the disease. These tumors can secrete histamine, prostaglandins, substance P, and 5-hydroxytryptamine.

Autonomic epilepsy is a rare disease thought to be the result of paroxysmal autonomic discharges. The blood pressure may fall or rise. There can be tachycardia, flush, and syncope.

Table 6
Differential Diagnosis of Anaphylaxis and Anaphylactoid Reactions

- Anaphylaxis and anaphylactoid reactions
  - Anaphylaxis and anaphylactoid reactions to exogenously administered agents
  - Physical factors
    - Exercise
    - Cold, heat, sunlight
  - Idiopathic
- Vasodepressor reactions
- Flush syndromes
  - Carcinoid
  - Postmenopausal
  - Chlorpropamide—alcohol
  - Medullary carcinoma thyroid
  - Autonomic epilepsy
- "Restaurant syndromes"
  - MSG
  - Sulfites
  - Scombroidosis
- Excess endogenous production of histamines
  - Systemic mastocytosis
  - Urticaria pigmentosa
  - Basophilic leukemia
  - Acute promyelocytic leukemia (tretinoin treatment)
  - Hydatid cyst
- Nonorganic disease
  - Panic attacks
  - Munchausen's stridor
  - Vocal chord dysfunction syndrome
  - Globus hystericus
- Other forms of shock
  - Hemorrhagic
  - Cardiogenic
  - Endotoxic
- Miscellaneous
  - Vancomycin-induced "red man syndrome"
  - Pseudoanaphylaxis
  - Hereditary angioedema

Many patients suffer from idiopathic flush. This occurs more frequently in women. It is associated with diarrhea, syncope, hypotension, and palpitations. There is no wheezing.

A group of postprandial syndromes can also produce reactions similar to anaphylactic events. They have been called the "restaurant syndromes." They can be the result of the ingestion of monosodium glutamate, sulfites, and saurine. Monosodium glutamate ingestion can cause chest pain, flushing, facial burning, sweating, dizziness, paresthesias, headaches, palpitations, nausea, and vomiting. Children also experience shivering

Probably the most common condition to be confused with anaphylaxis is a vasodepressor reaction. It can usually be distinguished from anaphylaxis by the absence of cutaneous symptoms and the presence of a bradycardia (however, anaphylaxis can occur with bradycardia). Serum tryptase may help in establishing the diagnosis. It can remain elevated for 2 h after the onset of symptoms of anaphylaxis.

and chills, screaming, irritability, and delirium. This has been referred to as the "Chinese Restaurant Syndrome." The exact mechanism of production of these events is unknown. However, it is thought that monosodium glutamate induces a "transient acetylcholinosis." Perhaps 15–20% of the population is sensitive to small doses of monosodium glutamate. However, these reactions can occur in any individual should the dose be large enough. Symptoms usually begin no later than 1 h after ingestion, but can be delayed in onset for up to 14 h. There may be a familial tendency to develop these reactions.

Sulfites are found in many foods, including dried fruits, gelatin, pickles, fruit, wine, fruit juices, sausages, and shellfish. In some individuals, the ingestion of sulfites produces flushing, hypotension, and bronchospasm. In many instances, bronchospasm is the only symptom. The bronchospasm can be profound.

Scombroidosis is the result of the ingestion of saurine, which is contained in spoiled fish. Saurine is a chemical with histamine-like activity. Bacteria, especially *Klebsiella pneumoniae* and *Proteus morgani*, contained in spoiled fish, decarboxylate histidine producing the saurine. Symptoms of scombroidosis are very similar to those seen in true anaphylactic events. They include flushing, urticaria and angioedema, pruritus, headache, and nausea and vomiting. A feature useful in distinguishing a true anaphylactic episode from scombroidosis is that everyone at the meal eating sufficient quantities of the fish experiences symptoms of scombroidosis. Isoniazid seems to predispose to such reactions.

Several symptoms are characterized by excessive endogenous production of histamine. These include mastocytosis, leukemias where there is an overproduction of histamine-containing cells (acute promyelocytic leukemia, basophilic leukemia), and hydatid cysts. Anaphylactic events can occur in such patients. For example, patients with systemic mastocytosis can experience anaphylactic episodes after the ingestion of opiates. Patients with promyelocytic leukemia can experience episodes after treatment with tretinoin.

Patients with emotional problems can express symptoms and signs that can be confused with anaphylaxis. Panic attacks are characterized by tachycardia, flushing, gastrointestinal symptoms, and shortness of breath. The absence of urticaria, angioedema, and hypotension are distinguishing features.

Two rare conditions that can sometimes be confused with anaphylaxis are vocal cord dysfunction syndrome and Munchausen's stridor. These have similar presentations. In the former, there is involuntary adduction of the vocal cords occluding the glottal opening. In the latter, there is intentional adduction of the vocal cords. In both instances, the patient will present with symptoms mimicking laryngeal edema with stridor. Patients with intentional vocal cord adduction (Munchausen's stridor) can be distracted from their stridor by asking them to perform such maneuvers as coughing.

Of course, other forms of shock must be considered during any acute event. These include hemorrhagic, cardiogenic, and endotoxic shock. These are usually easily distinguished from true anaphylactic or anaphylactoid episodes.

A group of miscellaneous disorders should be included in the differential diagnosis. One of these is the "red man syndrome" resulting from vancomycin administration. This can usually be eliminated, should vancomycin be required for therapy, by slowing the infusion rate of the drug.

A condition termed "pseudoanaphylaxis" has been described after the administration of procaine penicillin and lidocaine. In the case of penicillin, the reaction is thought to be the result of the procaine and not the penicillin. The manifestations are syncope and neurologic symptoms.

Occasionally patients with hereditary angioedema can have an evanescent, serpiginous rash during the first few hours of their attack. This rash, plus the accompanying symptoms of the attack, including abdominal pain and angioedema, can produce a picture similar to an anaphylactic episode.

The laboratory can be helpful in making a diagnosis of anaphylaxis and distinguishing an episode from other conditions. Of particular help in this regard is the determination of serum tryptase levels. The body's store of tryptase is limited to mast cells. Therefore, elevated serum tryptase levels are indicative of mast cell degranulation. The best time to measure serum tryptase is between 1 and 2 h after the onset of symptoms. Elevated tryptase levels usually return to normal within 2 h, but can be found as long as 5 h after onset of symptoms. In cases of protracted anaphylaxis, tryptase may remain elevated for as long as symptoms persist. On occasion, plasma or urine histamine determinations may be useful. Plasma histamine levels rise rapidly. They usually peak in 5–10 min and remain elevated for only 30–60 min. Thus, they are of little help if the patient is seen as long as an hour after the event. However, urinary histamine and its metabolites can be elevated for a longer duration of time and might be useful.

PREVENTION AND MANAGEMENT

Prevention—General Measures

Anaphylactic reactions are unfortunately an unavoidable aspect of the practice of medicine. However, their incidence and severity can be decreased by both general and specific measures (Table 7).

A thorough history for drug allergy should be taken in every patient. Proper interpretation of this history requires a knowledge of the immunologic and biochemical crossreactivity between drugs. Whenever possible a substitute, noncrossreactive drug should be administered. Oral administration is preferable to parenteral administration, since reactions are usually less severe after oral administration. When in-office parenteral administration of the drug is required, the patient should remain under observation for 20–30 min.

Patients at risk for anaphylaxis should carry appropriate identification. This can include a Medic Alert bracelet or necklace (Medic Alert, 2323 Colorado Ave., Turlock, CA, 95382. 1-800-432-5378) and an identification card in their wallet or purse. All such patients should be supplied with kits for the self-injection of epinephrine and instructed in the use of same. Any patient subject to anaphylactic episodes should not take β-

Table 7
Measures to Reduce the Incidence of Anaphylaxis and Anaphylactic Deaths

General measures
Obtain thorough history for drug allergy
Avoid drugs with immunological or biochemical crossreactivity with any agents to which the patient is sensitive
Administer drugs orally rather than parenterally when possible
Keep patients in office 20–30 min after injections
Check all drugs for proper labeling
Specific measures for patients at risk
Teach self-injection of epinephrine and caution patient to keep epinephrine kit with him or her
Have patient wear and carry warning identification
Discontinue β-adrenergic blocking agents, monoamine oxidase inhibitors, and ACE inhibitors in predisposed patients
Use preventive techniques when patient is required to undergo a procedure or take an agent that places them at risk. Such techniques include:
Pretreatment
Provocative challenge
Desensitization

adrenergic blockers, angiotensin converting enzyme inhibitors, or monoamine oxidase inhibitors. β-adrenergic blocking agents increase the risk of a severe episode and of course interfere with the activity of epinephrine. Angiotensin converting enzyme inhibitors prevent the compensatory response, consisting of the conversion of angiotensin I to angiotensin II, to hypotension. The administration of epinephrine can be contraindicated in patients taking monoamine oxidase inhibitors.

Prevention—Specific Measures

Latex

As noted, the incidence of anaphylaxis to latex is increasing. At particular risk are health care workers. Whenever possible latex-allergic patients should avoid contact with latex and, therefore, should use vinyl gloves. In addition, employees in the area should also use vinyl or powderless latex gloves. Patients allergic to latex will experience respiratory symptoms on inhalation of the powder from powdered latex gloves. All patients should wear and carry appropriate identification, and should be equipped with epinephrine self-injectors and trained in their use. Patients should also keep vinyl gloves with them in case they require emergency surgery and no such gloves are available. Such patients should take special care when visiting the dentist. If the dentist uses powdered gloves in his office, the patient should request the first morning appointment to reduce inhalation of powder. The dentist should use vinyl gloves and avoid latex dams while working on the patient.

Patients with latex allergy also have a high incidence of anaphylaxis to certain foods, including chestnuts and tropical fruits (bananas, kiwi, papaya, and so on). They should therefore be cautioned in this regard. Should such patients require surgery, the surgeon

and anesthesiologist should be informed of the allergy and appropriate operating room precautions should be instituted.

Plasma Exchange

Patients undergoing plasma exchange can experience anaphylaxis from multiple causes. The reported incidence is as high as 12%. Reactions can be owing to the apparatus used during the plasmapheresis procedure or to the plasma itself. Changing the plasmapheresis equipment may be helpful in preventing subsequent reactions. Pretreatment with prednisone and diphenhydramine can also be helpful. The pretreatment program consists of the administration of prednisone 50 mg po 13, 7, and 1 h prior to exchange and diphenhydramine 50 mg im 1 h prior to exchange.

Hemodialysis

Anaphylaxis and anaphylactoid reactions during hemodialysis have been attributed to a number of different factors. Ethylene oxide used for sterilization can produce an IgE-mediated anaphylactoid event. Other reactions have been related to the procedure used in processing the hemodialyzer. Reactions have been prevented by eliminating the use of reprocessed dialyzers, changing the hemodialysis membrane, changing the disinfectant process, and the discontinuation of washing hemodialyzers with hydrogen peroxide. Also, the type of membrane can be important. Severe reactions have been reported with the use of hollow fiber membranes made of cuprammonium cellulose. The use of ACE inhibitors during dialysis seems to predispose to anaphylactoid events. This is especially true when high-flux polyacrylonite (AN69) membranes are used.

When a patient experiences an anaphylactic or anaphylactoid reaction during hemodialysis, therefore, the type of membrane should be changed, no reprocessed membrane should be used, and ACE inhibitors and β-blockers should be discontinued if possible.

Idiopathic Anaphylaxis

A diagnosis of idiopathic anaphylaxis is made when an exhaustive search for etiologic agents has failed to identify a cause. A number of drugs have been used to prevent or reduce the severity of recurrent episodes of anaphylaxis in these patients. Such drugs include H_1 and H_2 antihistamines, oral albuterol, ephedrine, cromolyn sodium, and prednisone.

Patients with infrequent and mild episodes occurring three to four times a year probably need no preventive therapy. When episodes occur more frequently, such as six to eight times a year, the combination of an H_1 and H_2 antagonist is indicated. If the patient does not respond to this regimen, albuterol or ephedrine can be added. Cromolyn sodium administered orally has been shown to be effective in rare instances.

Some patients with this disorder experience recalcitrant, life-threatening episodes of anaphylaxis in spite of treatment with the above drugs. In these instances, prednisone can be used to prevent episodes. It has been reported that a dose of 60 mg a day with a gradual tapering over a period of several weeks is helpful. Most such patients can be managed on doses of 20 mg of prednisone or less every other day.

MANAGEMENT OF THE ACUTE EVENT

Drugs used to treat anaphylaxis and their suggested dosage regimen are seen in Table 8. Therapy may be divided into procedures that are performed immediately without extensive evaluation and those that are initiated after evaluation. These steps of therapy are listed in Table 9.

Rapid recognition with immediate treatment is essential. It is believed that prompt initiation of therapy prevents fatalities. It is important to stress that the steps seen in Table 9 are guidelines for therapy and are subject to the discretion of the physician managing the patient. Variations in the sequence and performance may be necessary dependent on physician judgment.

This discussion concerns the office management of anaphylaxis. The conditions that indicate transfer to a tertiary center depend upon the skill, experience, and assessment of the physician caring for the patient. Clearly, in order to initiate therapy, the proper medication and apparatus must be available. There is no established consensus regarding the preferred office inventory of drugs and equipment needed to treat anaphylaxis. However, a suggested inventory is seen in Table 10. Any such inventory, like the treatment of anaphylaxis, is subject to the judgment of the individual physician. The equipment and drugs noted herein are reasonably extensive and may not be needed in every situation or in every office.

The first step in the management of anaphylaxis is a rapid assessment of the patient's status with emphasis on evaluation of the airway and state of consciousness. If the airway is compromised, it should be secured immediately. Pulse and blood pressure should be obtained. The patient should be placed in the supine position with feet elevated. Modification of this Trendelenburg position may be necessary if the patient is wheezing. In addition, the increased intrathoracic pressure produced by this position can reduce the pressure gradient between the right atrium and inferior vena cava, thus limiting the benefit of increased venous return. Therefore, frequent monitoring of blood pressure and pulse is required. If the antigen responsible has been injected, a tourniquet should be placed proximal to the injection site. The tourniquet should be released every 5 min (for a minimum of 3 min) during treatment. The tourniquet should be used no longer than a total of 30 min. Oxygen should be started. An estimate of the patient's weight should be made to help guide dosage decisions.

Simultaneously with the above measures, epinephrine should be administered. The dose and route of administration of epinephrine depend on the severity of the reaction. In almost all instances, the im or sc route is preferred. In adults, the dose is 0.3–0.5 mL (0.3–0.5 mg). In children, the dose is 0.01 mL/kg (0.01 mg/kg). The initial dose can be repeated two to three times as needed at 10 to 15 min intervals.

Rarely, severe hypotension might require iv epinephrine administration. There is no established dose, and numerous regimens have been proposed for iv use. Intravenous use should be utilized only for severe cases of hypotension because of the greatly increased risk for arrhythmias. The amount administered depends on the severity of the episode and should be titered against the response. A suggested protocol is as follows: An iv preparation is prepared by diluting 1.0 mL (1.0 mg) of a 1:1000 aqueous epinephrine solution in 10 mL of normal saline. This 1:10,000 aqueous preparation can be administered in doses of 0.1–0.2 mL every 5–15 min depending on the response. In more critical situations, the iv dose can be increased.

Table 8
Drugs and Other Agents Used in the Treatment of Anaphylaxis and Anaphylactoid Reactions

Drug	*Dose and route of administration*	*Comment*
Epinephrine		
	1:1000 0.3–0.5 mL sc or im (adult); 1:1000 0.01 mg/kg or 0.1–0.3 mL sc or im (child)	Initial drug of choice for all episodes; should be given immediately. May repeat every 10–15 min
	0.1–1.0 mL of 1:1000 aqueous epinephrine diluted in 10 mL normal saline iv (*see text* for details)	If no response to sc or im administration and patient in shock with cardiovascular collapse
Antihistamines		
Diphenhydramine	25–50 mg im or iv (adult) 12.5–25 mg po, im, or iv (child)	Route of administration depends on severity of episode
Ranitidine or cimetidine	4 mg/kg iv cimetidine and 1 mg/kg iv ranitidine in adults.	Cimetidine should be administered slowly, since rapid administration has been associated with hypotension; dose in children not established.
Corticosteroids		
Hydrocortisone	100 mg to 1 g iv or im (adult) 10–100 mg iv (child)	Exact dose not established; other preparations, such as methylprednisolone, can be used as well; for milder episodes, prednisone 30–60 mg may be given (*see text*)
Drugs for resistant bronchospasm		
Aerosolized β-agonist (albuterol, metaproterenol)	Dose as for asthma (0.25–0.5 cc in 1.5–2 cc saline every 4 h, prn for albuterol)	Useful for bronchospasm not responding to epinephrine
Volume expanders		
Crystalloids (normal saline on ringers lactate)	1000–2000 cc rapidly in adults; 30 mL/kg in first hour in children	Rate of administration titrated against blood pressure response for iv volume expander; after initial infusion further administration requires tertiary care monitoring; in patients who are β-blocked, larger amounts may be needed
Colloids (hydroxyethyl starch)	500 mL rapidly, followed by slow infusion in adults	
Vasopressors		
Dopamine	400 mg in 500 cc; dextrose 5% in water as iv infusion; 2–20 μg/kg/min	Dopamine probably the drug of choice; the rate of infusion should be titered against the blood pressure response; continued infusion requires tertiary care monitoring
Levaterenol	4 mg in 500 cc dextrose (5%) in water as iv infusion; initial dose is 4–8 μg/min; in adults	
Drugs employed in patients who are β-blocked		
Atropine sulfate	0.3–0.5 mg iv; may repeat every 10 min to a maximum of 2 mg in adults	Glucagon is probably the drug of choice with atropine useful only for treatment of bradycardia
Glucagon	Initial dose of 1–5 mg iv followed by infusion of 5–15 μg/min titrated against blood pressure	

Abbreviations: sc—subcutaneous; im—intramuscular; iv—intravenous.

Table 9
Therapy of Anaphylaxis

Immediate action
Assessment
Check airway and secure if needed
Rapid assessment of level of consciousness
Vital signs
Treatment
Epinephrine
Supine position, legs elevated
Oxygen
Tourniquet proximal to injection site
Dependent on evaluation
Start peripheral iv fluids
H_1 and H_2 antagonist
Vasopressors
Corticosteroids
Inhaled β-adrenergic agent
Glucagon
Atropine
Electrocardiographic monitoring
Transfer to hospital
Hospital management
Medical antishock trousers
Continued therapy with above-noted agents and management of complications

Sublingual injection has been suggested when iv access cannot be obtained. The rationale for use of the sublingual route is based on the rich vascularity of this area. The 0.3–0.5 cc should be injected in the posterior one-third the sublingual area. If the antigen causing the episode was injected, 0.3 mL (0.1–0.3 mL in children) of a 1:1000 aqueous epinephrine solution can be injected into the original antigen injection site in order to slow absorption of antigen.

Antihistamine therapy should be considered adjunctive. Antihistamines should not be used as the sole form of therapy. They should be given with epinephrine. Based on the fact that histamine produces symptoms acting through a combination of H_1 and H_2 receptors, the administration of an H_1 and an H_2 antagonist may be superior to an H_1 antagonist alone. Diphenhydramine can be given intramuscularly or intravenously. The route of administration depends on the severity of the reaction. It can be given intramuscularly or intravenously. The dose in adults is 25–50 mg and in children is 12.5–25 mg. Ranitidine or cimetidine can be given intravenously in an adult. The dose of cimetidine in adults is 4 mg/kg and for ranitidine 1 mg/kg iv. Cimetidine should be administered slowly, since rapid administration can produce hypotension. There is no established dose in children.

The mechanism of action of corticosteroids in the treatment of anaphylaxis is unknown. In addition, corticosteroids probably do not exert any immediate effect. Nonetheless, it is believed that patients with anaphylactic episodes, especially those with severe symptoms, should receive glucocorticosteroid therapy. Perhaps the most

Table 10
Equipment and Medication for Therapy of Anaphylaxis in Office

Primary
Tourniquet
1- and 5-mL disposable syringes
Oxygen tank and mask/nasal prongs
Epinephrine solution (aqueous) 1:1000
Diphenhydramine injectable
Ranitidine or cimetidine injectable
Injectable corticosteroids
Ambu bag, oral airway, laryngoscope, endotracheal tube, no. 12 needle
Intravenous setup with large-bore catheter
Intravenous fluids, 2000 cc crystalloid, 1000 cc hydroxyethyl starch
Glucagon
Electrocardiogram
Normal saline 10-cc vial for epinephrine dilution
Supporting
Suction apparatus
Dopamine
Sodium bicarbonate
Aminophylline
Atropine
Optional
Defibrillator
Calcium gluconate
Neuroleptics for seizures
Lidocaine

important theoretical rationale for the use of corticosteroids involves the late-phase reaction. Since, as noted, anaphylaxis can be biphasic, prevention of the second phase is indicated. Although not documented to be effective in this regard, there is a theoretical rationale for their use. There is no established dose or drug of choice. Hydrocortisone can be given in a dose of 100 mg to 1 g intravenously or intramuscularly. For milder episodes, 50 mg of prednisone can be given orally. Wheezing unresponsive to epinephrine can be treated with an aerosolized β-adrenergic agent as in asthma.

Fluid replacement is essential therapy for the treatment of hypotension. As previously noted, hypotension is the result of a shift of fluid from the intravascular to extravascular space. Also, as noted, such patients may be maximally vasoconstricted owing to the compensatory formation of angiotensin II and the production of endogenous catecholamines. Therefore, the mainstay of treatment of hypotension, in addition to epinephrine, should be restoration of intravascular volume. This is best accomplished by the rapid administration of large volumes of fluid. Colloids or crystalloids can be used. Large volumes of crystalloids are often required. One thousand to 2000 cc of lactated ringers or normal saline should be given rapidly, depending on the blood pressure, at a rate of 5–10 mL/kg in an adult in the first 5 min. Children should receive up to 30 mg/kg of crystalloid solution in the first hour. A colloid can be substituted for crystalloid. The drug of choice is probably hydroxyethyl starch, since it is least likely to

Therapy

- Rapid recognition and early treatment with epinephrine is essential; other agents are employed in a way dictated by the presence of specific symptoms and signs; and
- Hypotension may be refractory to vasoconstrictor agents, and in this case, therapy should consist of rapid fluid volume replacement.

cause direct histamine release from mast cells and basophils. Adults should be given a rapid infusion of 500 mL followed by slow infusion thereafter.

Patients taking β-adrenergic blockers present a difficult problem regarding the management of hypotension. Such patients are resistant to vasoconstrictors and may require very large amounts of fluids. Five to seven liters may be necessary before stabilization occurs.

Vasopressors can be helpful, especially in patients not maximally vasoconstricted. The drug of choice is probably dopamine administered at a rate of 2–20 μg/kg/min. The rate should be titrated against the blood pressure.

Once again, patients taking β-blockers present a special problem. They can be resistant to standard therapeutic regimens. They have both inotropic and chronotropic cardiac suppression, and can experience marked hypotension and bradycardia. Two drugs, atropine and glucagon, have been recommended for therapy in such patients. Atropine is useful only for bradycardia. It does not exert a beneficial effect on the inotropic function of the heart. The dose of atropine is 0.3–0.5 mg every 10 min to a maximum of 2 mg. Glucagon, a polypeptide hormone produced by the α-cells of the pancreas, exerts both a positive inotropic and chronotropic effect. The inotropic effect is not dependent on catecholamines or their receptors, and is therefore unaltered by β-adrenergic blockade. Thus, glucagon may be the drug of choice in patients who are β-adrenergically blocked. The dose of glucagon is 1–5 mg intravenously as a bolus followed by infusion of 5–15 μg/min titrated against the clinical response. Beneficial effects are usually noted in 1–5 min and are maximal at 5–15 min following a bolus. Nausea and vomiting are the major limiting factors.

Because of the possibility of a biphasic episode, any patient with moderately severe anaphylaxis should be observed for several hours before discharge. There is no established period of observation, but it would appear reasonable that a minimum of 2 h for mild episodes and perhaps as long as 24 h for severe episodes is indicated.

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6 Insect Sting Allergy

Robert E. Reisman, MD

CONTENTS

INTRODUCTION

Allergic reactions to insect stings are a very common and, on occasion, a serious medical problem. The incidence of anaphylaxis in the general population has been estimated to range from 0.3–3%. Vital statistic registry data document at least forty deaths/yr as a result of insect sting anaphylaxis with the likelihood that other episodes of unexplained sudden death are also the result of insect stings. Individuals at risk are often very anxious about further stings and, as a result, make significant changes in their lifestyles.

In recent years, particularly since the availability of purified venoms for diagnosis and therapy, major advances have occurred. The natural history of insect sting allergy is now understood, and tools are available for appropriate diagnosis and treatment of individuals at risk for insect sting anaphylaxis. For many individuals, this is a self-limited disease, and for others, treatment results in a permanent "cure."

INSECTS

The stinging insects are members of the order Hymenoptera of the class Insecta. They may be broadly divided into two families; the vespids, which include the yellow jacket, hornet, and wasp, and the Apids, which include the honeybee and bumblebee. People may be allergic to one or all of the stinging insects. The identification of the culprit insect responsible for reactions is thus important in terms of specific advice and specific venom immunotherapy discussed below.

From: *Allergic Diseases: Diagnosis and Treatment*
Edited by P. Lieberman and J. Anderson Humana Press Inc., Totowa, NJ

- Insects most commonly responsible for allergic reactions are yellow jackets, wasps, hornets, bees, and fire ants.
- Estimates of the incidence of anaphylaxis to insect stings range as high as 3% of the general population.
- The test of choice to identify individuals at risk of a repeat reaction and the species of insect responsible for previous reactions is the allergy skin test.

The presence of the different stinging insects varies in different parts of the country. For example, the wasp is most common in Texas, and honeybees may be more common in farm areas where they are used for plant fertilization.

The yellow jacket is the most common cause for allergic reactions resulting from insect stings. These insects primarily nest in the ground and are easily disturbed in a course of activity, such as lawn mowing and gardening. They are also attracted to food, and are thus commonly found around garbage and picnic areas. Yellow jackets are particularly present in the late summer and fall months of the year. Hornets, which are closely related to the yellow jacket, nest in shrubs and also are easily provoked by such activities as hedge clipping. Wasps are found in nests usually hanging from eaves. In general, there are few wasps per nest, and thus stings are relatively uncommon in most of the country. The honeybee hive may contain thousands of honeybees. As a rule, these insects are quite docile, as exemplified by the common picture of the beekeeper handling thousands of bees on his face or other parts of the body. However, if the honeybee hive is disturbed, multiple stings may occur. The bumblebee, which is a solitary bee, is a rare cause for an insect sting reaction.

The problem of multiple insect stings has recently been intensified by the introduction of the "Africanized" honeybee, the so-called killer bee, into the southwestern United States. The African honeybee was introduced into Brazil from Africa in 1956 for the purpose of providing a more productive bee in tropical climates. These bees are much more aggressive than domesticated European honeybees, which are found throughout the United States. The African honeybee has interbred with the European honeybee, but unfortunately, the aggressive characteristics have persisted. These bees are extremely aggressive, and massive stinging incidents have occurred, resulting in death from venom toxicity. The Africanized honeybees entered South Texas in 1990, and are now present in Arizona and California. It is anticipated that these bees will continue to spread throughout the southern United States. They are unable to survive in colder climates, but may make periodic forays into the northern United States during the summer months.

The fire ant, which is a nonwinged stinging insect, is found in the southeastern and south central United States primarily near the Gulf Coast. These insects are gradually spreading northward and westward, and it is anticipated will extend as far north as Virginia and eventually reach Arizona, New Mexico, and California. The fire ant is increasingly responsible for allergic reactions. It attaches itself by biting with its jaws. It then pivots around its head and stings at multiple sites in a circular pattern. Within 24 h a sterile pustule develops, which is diagnostic of the fire ant sting.

In contrast to stinging insects, biting insects, such as the mosquito, rarely cause serious allergic reactions. These insects deposit salivary gland secretions, which have no re-

lationship to the venom deposited by stinging insects. Anaphylaxis has occurred from bites of the deer fly, kissing bug, and bed bug. Isolated reports also suggest that on rare occasions mosquito bites have caused anaphylaxis. It is much more common, however, for insect bites to cause large local reactions, which may have an immune pathogenesis.

REACTIONS TO INSECT STINGS

Normal Reaction

Insect stings, in contrast to insect bites, always cause pain at the sting site. The usual or "normal" reaction is this localized pain, swelling, and redness. This reaction usually subsides within a few hours. Little treatment is needed other than analgesics and cold compresses.

Large Local Reactions

Extensive swelling and erythema, extending from the sting site over a large area, is fairly common. The swelling usually peaks in 24–48 h, and may last 7–10 days. For example, a sting on the hand may cause swelling extending as far as the elbow. On occasion, when severe, fatigue, nausea, and malaise may be present. If mild, these large local reactions can be treated with aspirin and antihistamines. When severe or disabling, steroids, such as prednisone, 40 mg daily for 2–3 d, are very helpful in diminishing the swelling. There is no documentation that the application of papain (meat tenderizer) or "mud" alleviates local swelling. These large local reactions have been confused with infection and cellulitis. Insect sting sites are rarely infected and antibiotic therapy rarely indicated. Tetanus prophylaxis is unnecessary.

The natural history of reactions that occur following subsequent restings in individuals who have had large local reactions has been well studied. After subsequent stings, large local reactions tend to reoccur in about 80% of individuals. The risk for subsequent insect anaphylaxis is very low, <5%. Thus, individuals who have had large local reactions are not considered candidates for venom immunotherapy (discussed below) and do not require venom skin tests.

Anaphylaxis

There are no clinical criteria or risk factors that identify individuals at potential risk for insect sting anaphylaxis other than a history of a prior anaphylactic reaction. The clinical features of anaphylaxis following an insect sting are similar to anaphylaxis from other causes. The most common symptoms are dermal, generalized urticaria, flushing, and angioedema. The most severe symptoms, which may be life-threatening, include respiratory distress owing to asthma and upper airway swelling, circulatory collapse, and shock. Other symptoms include nausea, bowel cramps, diarrhea, rarely uterine cramps, and a feeling of "impending doom." Anaphylactic symptoms usually start immediately after a sting, within 10–30 min. On rare occasions, reactions have started after a longer time interval.

Estimates of the incidence of anaphylaxis in the general population range as high as 3%. The majority of reactions have occurred in individuals under the age of 20, with a 2:1 male to female ratio. These prevalence data probably reflect exposure rather than any specific age or sex predilection for anaphylaxis. Although the majority of insect

sting reactions occur in younger individuals, severe anaphylaxis may occur at any age. Most deaths have occurred in older individuals, many of whom had cardiovascular disease.

The natural history of insect sting anaphylaxis has been the subject of fairly intense investigation. Individuals who have had insect sting anaphylaxis have an approx 60% recurrence rate of anaphylaxis after subsequent stings. Viewed from a different perspective, not all individuals presumed to be at risk react to re-stings. The incidence of these resting reactions is influenced by age and severity of the initial anaphylactic reaction. In general, children are less likely to have resting reactions as compared to adults. The more severe the anaphylactic reaction, the more likely it is to reoccur. For example, children who have had dermal symptoms as the only manifestation of anaphylaxis have a remarkably low resting reaction rate. On the other hand, individuals of any age who have had severe anaphylaxis have an approx 80% likelihood of repeat reactions. When anaphylaxis does reoccur, the severity of the reaction tends to be similar to the initial reaction. No relationship has been found between the occurrence and degree of anaphylaxis and the intensity of venom skin test reactions.

Unusual Reactions

Serum sickness-type reactions, characterized by urticaria, joint pain, and fever, have occurred approx 7 d after an insect sting. Individuals who have this reaction are subsequently at risk for acute anaphylaxis after repeat stings and thus are considered candidates for venom immunotherapy.

There have been isolated reports of other reactions, such as vasculitis, nephritis, neuritis, and encephalitis, occurring in a temporal relationship to an insect sting. The specific etiology for these reactions has not been established, and in general, venom immunotherapy is not indicated.

Toxic Reactions

Many simultaneous insect stings, such as 100 or more, may lead to toxic reactions owing to venom constituents. The clinical symptoms that characterize these reactions are primarily cardiovascular and respiratory in nature. Immediate treatment is directed to cardiovascular and respiratory support. Following toxic reactions, individuals may develop IgE antibody and may then be at risk for subsequent allergic sting reactions. Thus, individuals who have had toxic reactions should be tested for the possibility of potential sensitization and need for specific therapy. The frequency of these toxic reactions has increased because of the Africanized honeybees.

ALLERGY TESTS

Acute allergic reactions from insect stings are the result of IgE antibodies reacting with insect venoms. These antibodies are best detected by the immediate skin test reaction. Individual insect venoms, yellow jacket, honeybee, white faced hornet, yellow hornet, and wasp, are commercially available for diagnostic skin tests. A positive skin test is defined as an immediate wheal and flare reaction occurring within 10 min after an intradermal skin test with venom doses up to 0.1–1.0 μg/mL. Higher venom doses cause nonspecific irritative reactions. IgE antibodies in the serum can also be mea-

sured by the radioallergosorbent test (RAST). This in vitro test is more expensive and generally much less sensitive than the simple immediate skin test. It is estimated that approx 20% of individuals with positive venom skin tests will not have a positive RAST. Thus, the RAST is not recommended for routine diagnosis unless a skin test cannot be performed.

At the present time, fire ant venom is not available. The commercial whole-body fire ant extract is reasonably reliable for skin test diagnosis and immunotherapy for fire ant-allergic individuals.

THERAPY

Acute Reaction

The immediate medical treatment for acute anaphylaxis owing to insect stings is the same as that for anaphylaxis from any other cause. This treatment is detailed in Chapter 5.

If the insect stinger remains in the skin, it should be gently flicked off, with care taken not to squeeze the sac. Unfortunately, the majority of the venom is deposited very quickly after the sting, and removal of the sac will only be helpful if done immediately.

Prophylaxis

Individuals who have had insect sting anaphylaxis and have positive venom skin tests are at risk for further reactions after restings. Prophylactic measures include advice to minimize potential exposure, available medication for immediate treatment of anaphylaxis, and consideration of venom immunotherapy.

Measures that might minimize insect stings include wearing protective clothing when outside, such as shoes, slacks, long sleeves, and gloves. Cosmetics, perfumes, and dark colored clothing, which attract insects, should be avoided. Great care should be taken when eating outdoors, since food and garbage do attract insects.

The primary medication for treatment of anaphylaxis is epinephrine. Individuals at potential risk should be given epinephrine, available in preloaded syringes (Ana-Kit, Bayer Laboratories Spokane, WA; Epi-Pen™ and Epi E-Z Pen™, Center Laboratories, Port Washington, NY). Antihistamines, such as diphenhydramine, are also recommended and may be helpful for treatment of hives and edema.

VENOM IMMUNOTHERAPY

Injection of purified venoms (venom immunotherapy) is an extremely effective treatment for individuals at risk for venom anaphylaxis. The overall success rate in preventing subsequent anaphylaxis is over 98%. Venom immunotherapy reduces the risk for anaphylaxis from approx 50–60% in untreated individuals to about 10% after 2 yr of therapy and to about 2% after 3–5 yr of treatment. The guidelines for selection of individuals for treatment and venom immunotherapy dosing are now well established and are outlined in Tables 1–3.

- Patients at risk of a future systemic (anaphylactic) reaction should carry epinephrine, be instructed in avoidance techniques, and receive immunotherapy.
- Patients who are candidates for immunotherapy are adults with any form of anaphylactic reaction and children whose previous anaphylactic episode extended beyond cutaneous manifestations only.
- The success rate of venom immunotherapy is better than 98%.

Selection of Individuals (Table 1)

All individuals who have severe symptoms of anaphylaxis and have positive venom skin tests should receive venom immunotherapy. Children who have had very mild reactions with dermal symptoms only do not require therapy. Their families should be advised to keep epinephrine and antihistamines available. Adults who have had similar mild anaphylaxis can probably be treated in a similar fashion, but there is less evidence to support this practice in adults than in children. Currently, venom immunotherapy is still recommended for these adults. Those individuals who have had reactions of moderate intensity, such as mild asthma, nausea, and urticaria, without serious life-threatening reactions, might also be treated without immunotherapy and with the availability of emergency medication. They are likely to have similar moderate reactions to subsequent stings. This decision is influenced by other factors, such as risk of a exposure, other disease processes, such as cardiac disease, and medication use.

Following serum sickness reactions, individuals usually have positive skin tests and are then at risk for subsequent anaphylaxis. These observations are similar to the classic horse serum induced serum sickness. If skin tests are positive, these individuals should then receive immunotherapy. Because venom is a highly sensitizing agent, individuals who have had toxic reactions may develop IgE antibody and then are at potential risk for anaphylaxis. In that situation, immunotherapy is indicated. As already noted, individuals with large local reactions are not candidates for venom immunotherapy.

Venom Selection

The product brochure, which has not changed since the availability of commercial venoms in 1979, recommends venom immunotherapy with each venom that elicits a positive skin test reaction. Studies of venom antigenic crossreactivity explain the common observation of multiple positive venom skin tests despite only one insect sting reaction. For example, an individual who has had an allergic reaction following a yellow jacket sting will almost always have positive skin tests to hornet venom and possibly a positive skin test to wasp venom. Awareness of this crossreactivity allows more selective venom treatment. The selection of venom for therapy is based on a history of the culprit insect responsible for the reaction and the degree of skin test reactivity. This approach utilizing single venoms despite multiple positive skin tests is less expensive, requires fewer injections, and is therapeutically as effective.

Dosing Schedule (Tables 2 and 3)

Venom immunotherapy is initiated with injection of small doses of venom followed by increasing doses until the recommended maintenance dose has been reached. The initial dose of venom is based on the degree of skin test reactivity, not the severity of the

Table 1
Indications for Venom Immunotherapy in Patients with Positive Venom Skin Tests[a]

Insect sting reaction	*Venom immunotherapy*
"Normal"—transient pain, swelling	No
Extensive local swelling	No
Anaphylaxis	
Severe	Yes
Moderate	Yes[b]
Mild; dermal only	
Children	No
Adults	Yes[b]
Serum sickness	Yes
Toxic	Yes

[a]Venom immunotherapy is not indicated for individuals with negative venom skin tests.

[b]Patients in these groups might be managed without immunotherapy. *See text.*

Table 2
General Venom Immunotherapy Dosing Guidelines

Initial dose	.01–0.1 μg, depending on degree of skin test reaction	
Incremental doses	Schedules vary from "rush" therapy administering multiple venom injections over several days to traditional once weekly injections	
Maintenance dose	50–100 μg of single venoms, 300 μg of mixed vespid venom	
Maintenance interval	4 wk	1st yr
	6 wk	2nd yr
	8 wk	3rd yr
Duration of therapy	Stop if skin test becomes negative	
	Finite time, 3–5 yr (*see text*)	

anaphylactic reaction. Incremental doses are given according to a number of schedules, ranging from single doses once weekly to rush immunotherapy, which utilizes multiple doses over a 2–3 d period. A typical dose schedule is shown in Table 3. Maintenance doses of 100 μg of single venoms or 300 μg of a mixed vespid preparation (yellow jacket, white faced hornet, yellow hornet) is the traditional recommendation. Recent studies indicate that top doses of 50 μg of individual venoms are effective. Once the maintenance dose is reached, injections are usually given at 4-wk intervals through the first year and then 6- and 8-wk intervals after the second and third year, respectively.

Table 3
Representative Examples of Venom Immunotherapy Dosing Schedules[a]

	Traditional	*Modified rush*	*Rush*	
Day				
1	0.1	0.1	0.1[c]	3.0
		0.3	0.3	5.0
		0.6	0.6	10
			1.0	
Day 2			20	
			35	
			50[b]	
			75	
Day 3			100	
Week				
1	0.3	1.0		
		3.0		
2	1.0	5.0	100	
		10	Repeat every 4 wk	
3	3.0	20		
4	5.0	35		
5	10	50[b]		
6	20	65		
7	35	80		
8	50[b]	100		
9	65			
10	80	100		
11	100	Repeat every 4 wk		
12				
13	100			
	Repeat every 4 wk			

[a]Starting dose may vary depending on patients' skin test sensitivity. Subsequent doses modified by local or systemic reactions. Doses expressed in micrograms.

[b]Fifty micrograms may be used as top dose.

[c]Sequential venom doses administered on same day at 20- to 30-min intervals.

Reactions to Venom Immunotherapy

Systemic Allergic Reactions

Systemic allergic reactions owing to venom immunotherapy are relatively uncommon, as compared to reactions that follow other types of allergen immunotherapy. However, because of the possibility of such reactions, it is important that venom immunotherapy, as with other allergenic extracts, should only be administered in the setting in which personnel and equipment are available for treatment of an anaphylactic reaction. Following such a reaction the venom dose is usually decreased about 25–33% and subsequent doses given at lesser increasing increments. If the patient is receiving several different venoms, it is prudent only to give one venom at each treatment time or separate the time of dosing. Inability to ultimately tolerate a maintenance venom dose is rare.

Local Reactions

Large local reactions following venom immunotherapy are more common. When other types of allergenic extracts are administered, doses are decreased and a smaller dose might be maintained to avoid such reactions. In the case of venom, however, it is necessary to administer a maintenance dose (50–100 μg) in order to assure protection from insect stings. Measures to minimize these local reactions include splitting the venom dose into two injection sites and the addition of a small amount of epinephrine, such as .05–0.1 mL, with the venom, a commonly used procedure, although its efficacy has never been documented. When these local reactions are extensive and particularly somewhat delayed in onset, there may be accompanying nausea and fatigue. In this situation, the addition of a small amount of steroid, such as betamethasone, 0.05–0.1 mL, to the venom may markedly reduce such reactions.

Fatigue, Malaise

Unusual symptoms that have been reported after venom injections, and also have occurred after other types of allergenic solutions, such as dust and mold, are symptoms of fatigue, nausea, malaise, and even fever. These symptoms usually start several hours after the venom injection and may last 1–2 days. The concomitant administration of aspirin with the venom injection and then further aspirin doses for the next 24 h may eliminate these reactions. If the reactions persist despite aspirin, then a small dose of oral steroids, such as 20 mg prednisone, given with the venom dose and repeated once in 6–8 h has been very helpful.

Long-Term Therapy

There have been no reported adverse reactions from long-term venom immunotherapy.

Pregnancy

Venom injections appear to be safe for use during pregnancy.

Monitoring During Venom Immunotherapy

Venom Skin Tests

In a small minority of venom-treated patients, the venom skin test does become negative. The loss of skin test reactivity indicates that venom-specific IgE is not present, and thus, the need for continued venom treatment is unnecessary (discussed below). As a general rule, it is reasonable to retest individuals with venom every 1–2 yr to examine this possibility.

Measurement of Serum Venom-Specific IgG

Venom-specific IgG has been associated with immunity to insect stings. During the course of venom immunotherapy, venom- specific IgG is stimulated. Suggestions have been made that individuals receiving venom immunotherapy should have serial monitoring of this antibody titer, and those individuals who have failed to develop adequate titers should have a modification in dosing. In my opinion, careful review of these data does not support that recommendation. Since venom immunotherapy is 98% effective in preventing subsequent sting reactions, it does not seem reasonable to monitor any type of immune parameter, looking for possible treatment failures. In addition, the pub-

lished data do not indicate that for an individual patient, there is that close a correlation between absolute antibody titers and the success of venom immunotherapy.

Treatment Failures

Persistent allergic reactions following insect stings in individuals receiving venom immunotherapy are most uncommon. As noted above, the success rate of venom immunotherapy is better than 98%. When these reactions do occur, it is first necessary to determine whether the patient has been treated with the correct venom. This might require reassessment by history and repeat skin tests. If other insects are suspect, then venom immunotherapy should be modified.

If it appears that the patient is receiving the correct venom, then the dose of the venom must be increased. For example, if the individual is receiving 100 μg of venom, the dose should be increased to 150–200 μg.

Cessation of Venom Immunotherapy

Definitive criteria for safe cessation of venom immunotherapy are being evolved. These include immunologic criteria and a specific period of treatment, unrelated to the persistence of IgE antibody.

Conversion to a Negative Skin Test

Conversion to a negative skin test is an absolute criterion for stopping therapy, indicating that the IgE antibody, the immune mediator of this reaction, is no longer present. In our experience, approx 20% of individuals will convert to a negative skin test after 3–5 yr of therapy.

Fall in Serum Venom Specific IgE to Insignificant Titer

An allergy skin test is a very sensitive test. For example, individuals with "burned out" ragweed hay fever may have a persistent positive skin test for many years. For this reason, we examined the relationship of the serum venom-specific IgE titer as a criterion for stopping treatment. When treatment was discontinued because of a fall in serum-specific IgE to undetectable levels, the resting reaction rate was about 10%/patient. The average time of treatment was about 2 yr. Interestingly, the control for these studies was a group of patients who stopped by self-choice. The resting reaction rate in this group, who received treatment for approximately the same time period, was also about 10%. These data suggested that after 2 yr of treatment, the risks of allergic reactions from restings do diminish to about 10%.

Specific Time Period

Treatment for a specific period of time, 3–5 yr, despite the presence of a persistent positive skin test, also appears to be an adequate criterion for stopping therapy. Two European studies suggest that 3 yr of venom immunotherapy are sufficient. Studies in children and adults at Johns Hopkins University concluded that 5 yr of therapy are adequate.

Specific Time Period of Treatment Related to the Nature of the Anaphylactic Symptoms

We have also examined the possibility that a specific period of time of treatment is adequate and related these observations to the nature of the initial anaphylactic reaction.

These data suggest that individuals who have had mild to moderate venom anaphylactic symptoms can discontinue treatment after 2–3 yr. Patients who have had more severe anaphylaxis may require longer periods of time. In that group, the resting reaction rate, after cessation of therapy, was about 15%, with the majority of the patients having similar severe anaphylactic symptoms. These observations suggest that it may be prudent to treat individuals who have had more severe allergic reactions, such as loss of consciousness, hypotension and shock, and retain positive skin tests, for longer periods of time.

CONCLUSION

In summary, although problems remain, such as prediction or selection of individuals at potential risk for initial anaphylaxis and issues regarding duration of treatment, the understanding and approach to treatment of individuals with insect sting allergy have been defined and for the majority of individuals, effective treatment is available.

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7 Evaluation and Treatment of the Child with Asthma

Gail G. Shapiro, MD, C. Warren Bierman, MD, and Frank S. Virant, MD

CONTENTS

INTRODUCTION

Asthma is a pulmonary disorder characterized by reversible periods of airway obstruction, bronchial hyperresponsiveness, and associated airway inflammation. A comprehensive approach to asthma therapy in children should include assessment of disease severity and scrutiny for exacerbating factors followed by appropriate environmental modifications as well as pharmacotherapy. Long-term successful management is clearly linked to education of patients and their parents about asthma, proper use of medication, and a plan of action for periods of exacerbation.

When presented with a history of chronic cough or wheezing in a child, a thorough history and directed physical examination should reduce the differential diagnoses to only a few considerations (*see* Table 1). Historically, the appearance of symptoms shortly after birth greatly increases the likelihood of a congenital abnormality as a

From: *Allergic Diseases: Diagnosis and Treatment*
Edited by P. Lieberman and J. Anderson Humana Press Inc., Totowa, NJ

Table 1
Differential Diagnosis of Asthma[a]

α-1 Antitrypsin deficiency
Asthma
Bronchiectasis
Bronchiolitis
Bronchopulmonary dysplasia
Congenital anomalies
Cystic fibrosis
Foreign body (nasal, tracheal, bronchial)
Gastroesophageal reflux
Laryngeal webs
Laryngotracheobronchitis
Laryngotracheomalacia
Pertussis
Pulmonary eosinophilia
Pulmonary hemosiderosis
Pulmonary hypersensitivity diseases (e.g., mold, fibers)
Pulmonary interstitial emphysema
Stenosis (tracheal, bronchial)
Toxic inhalations
Tracheoesophageal fistula
Tumor
Vascular rings

[a]From ref. *2*.

source for symptoms, such as vascular rings, laryngeal webs, tracheostenosis, or bronchiostenosis. The abrupt onset of coughing or wheezing in a young child, often associated with eating and in the absence of concurrent airway infection, should be considered secondary to foreign body aspiration until proven otherwise. Gastroesophageal reflux (GER) should be considered in any infant with postprandial vomiting or nocturnal cough, or in an older child who has associated complaints of dysphagia or heartburn. The combination of recurrent sinobronchitis, failure to thrive, and chronic malabsorption associated with chronic cough and wheezing suggests the possibility of cystic fibrosis.

The probability of asthma as the diagnosis is greatly increased with a positive family history for atopy or other family members with asthma. In a child with obvious asthma, signs of atopy, including eczema, episodic urticaria, recurrent middle ear effusion, and rhinitis, increase the probability that allergy plays a significant role in chronic airway symptoms. It is also useful to ask about possible exacerbating factors for symptoms, including allergens, irritants, drugs, cold air, and exercise.

There are three important elements in the evaluation of the patient with asthma: the history, the physical examination and measurement of pulmonary function.

HISTORY

The history should uncover the evolution of symptoms over days, months, or years, specific days of the week, and time of day, with an eye toward associations, such as sea-

Key Features of Asthma

- Reversible airway obstruction
- Bronchial hyperresponsiveness
- Airway inflammation
- Familial tendency
- Association with allergy: children more than 2 yr of age: 80%; adults: 50%

sonality, visits to homes with pets, times of respiratory infections, and physical activity. Is the problem episodic or continual? If episodic, how often are the episodes, and are they truly isolated or rather acute bursts connected by more subtle symptoms of disease? Are there specific cause-and-effect associations or trigger factors? These should be clarified so that their avoidance can be incorporated in a management plan. Have there been emergency room visits, hospitalizations, or need for intubation and assisted ventilation? Have these problems occurred in the face of appropriate medication, or has the patient been undertreated?

Symptoms vary with age. The infant and young child may have histories of recurrent bronchitis or pneumonia, persistent coughing with colds, recurrent "croup," or just a chronic "chest rattle." Older children and adolescents often develop "tight" chests with colds, recurrent "chest congestion," "bronchitis," or persistent coughing or wheezing. Respiratory symptoms may be precipitated or exacerbated also by exposure to animals, moldy or dusty areas, tobacco smoke, cold air, or by exercise.

The past medical history and review of systems often clarifies the clinical picture. If the patient had food allergy and eczema in infancy, allergy will probably remain an important factor. One needs to inquire about such allergic manifestations as gastrointestinal problems, including vomiting or diarrhea; skin conditions, such as atopic dermatitis or hives; and the presence or absence of such factors as perennial or seasonal nasal obstruction, frequent respiratory and ear infections, and exercise intolerance. One needs to ask specifically about factors that may aggravate symptoms, such as exposure to house dust, animals, grass cuttings, and irritants, such as aerosol sprays and cigaret smoke, or reactions to outdoor pollutants. Drug reactions are particularly important, especially idiosyncratic or allergic reactions to antibiotics, aspirin and other nonsteroidal anti-inflammatory drugs, bronchodilators, or antihistamines. One should also inquire about unusual reactions to insect stings and about hospitalizations. Details about whether the patient had previously had an allergy-related workup with studies for specific IgE identification and immunotherapy (hyposensitization), and lung function assessment should be recorded.

The environmental history is a unique and important element in the patient with suspected asthma, since many of the symptoms may be exacerbated by factors found in the surroundings, whether home, school, day care, work, or play. The environmental history is of importance primarily because it provides information on potential allergens to which the patient is exposed, and it is the cornerstone of therapy in terms of avoidance of specific factors that may be identified by allergy testing. In patients of all ages, it is very important to ask about cigaret smoking or exposure to secondhand tobacco smoke.

PHYSICAL EXAMINATION

The physical examination may be dramatic or unrevealing. It begins with an overall visual impression and should include at least an assessment of the head, neck, chest, and skin, but other systems as well, if indicated by the history. If the patient is experiencing an acute episode of airway obstruction, it is common to note anxiety, dyspnea, and increased respiratory rate. There may be audible wheezing and cough. None of this is apparent between acute episodes. If chronic obstruction has been long-standing, one may see a bowing of the ribs and an increased anterior–posterior diameter, since growth and bony remodeling will accommodate chronic pulmonary hyperinflation. On auscultation, one may notice increased expiratory phase of respiration. There may be wheezing on expiration or on both inspiration and expiration; coarse wheezes may take on the quality of rhonchi. Rales typically indicate parenchymal disease, however, they may also be present if there is localized atelectasis, common with asthma. Sudden deterioration and absence of breath sounds suggest the rare complication of pneumothorax. More common is crepitus and extrapulmonary dissection of air with apparent edema extending upward from the chest into the neck and face owing to dissecting pneumomediastinum, usually a spontaneously resolving event, but one that suggests severe obstruction.

The head and neck examination is often abnormal in patients with asthma. Children may show evidence of middle ear disease, which may be a complication of allergic rhinitis: middle ear fluid, otitis, or ventilating tubes. In both children and adults, the eyes may show conjunctival edema and injection compatible with allergic disease. There may be periorbital edema and discoloration owing to the venous and lymphatic stasis that may accompany allergic rhinitis (so-called allergic shiners). The nose may show the pallor, edema, and clear secretions of allergic rhinitis or erythema and purulent secretion from infectious rhinitis or sinusitis. The presence of nasal polyps in children suggests cystic fibrosis, whereas in the adolescent and adult, it suggests nonallergic eosinophilic disease (possibly with aspirin sensitivity) that may involve the upper and lower airway. Since sinusitis and viral upper respiratory infections both exacerbate asthma, it is important to diagnose and treat those problems that are likely to be bacterial. Skin manifestations of atopy, such as the lichenification and flexor crease rash of atopic dermatitis (eczema), frequently precedes the onset of chronic asthma.

LABORATORY EVALUATION (*SEE* TABLE 2)

Lung Function Tests

Lung function tests are objective, noninvasive, and cost-effective in diagnosing and following the patient with asthma. A simple mechanical spirometer or a Wright Peak Flow Meter (pediatric meters are available for younger children) is useful in office practice. Children as young as 4 yr old can be taught to perform pulmonary function maneuvers with birthday party favors that make whistle sounds to reinforce forced expiration. Results can be compared with normal standards.

Spirometry involves certain pitfalls, but adequate results generally can be obtained from children over 5 yr of age. The best of three forced expiratory tracings should be used as the best estimate of a patient's pulmonary function. Coaching and teaching are

Confirmation of Asthma Diagnosis

- Difficult to confirm below the age of two because of "wheezing/congestion" associated with viral infection
- Asthma is a chronic condition; documentation of repeated clinical episodes of respiratory distress, which responds to bronchodilators, is helpful information
- Office pulmonary function test results are helpful objective information after the age of 5 yr
- Response to bronchodilators, which document reversible pulmonary obstruction: FEV_1: 15–20%; FEF_{25-75}: 20–25%
- Exercise tolerance in some cases, and methacholine/histamine challenges in select cases by a specialist may be necessary to confirm diagnosis

required for the patient to achieve good technique. If the curves that are generated do not fit the clinical picture, one must look at the quality of data entry and technique before assuming that there is lung disease. Spirometry may be expressed with flow volume curves rather than time volume curves. Flow volume loops include a tracing for inspiratory flow. This is helpful for distinguishing extrathoracic from intrathoracic obstruction. When patients are uncooperative or unable to learn proper spirometric technique, body plethysmography can be used, generally available in hospital pulmonary function laboratories.

Response to Bronchodilators

A straightforward diagnostic test for asthma is to look for an improvement in lung function before and after administration of bronchodilators, preferably β-2 agonists (inhalation of two actuations of albuterol or equivalent by pressurized metered dose inhaler or 0.1–0.15 mg/kg aerosol solution of albuterol [5 mg maximum], or epinephrine injections [epinephrine hydrochloride 1:1000], 0.01 mL/kg up to a maximum dosage 0.3 mL subcutaneously). A >15% improvement in forced expiratory volume in 1 s (FEV_1) is virtually diagnostic of asthma. If there is a lack of improvement in FEV_1, it does not necessarily rule out asthma. With severe airway inflammation, a 1–2 wk course of oral corticosteroids may be necessary to demonstrate a reversible component to airflow obstruction. With mild disease, lung function will be normal unless the patient is experiencing an exacerbation.

Exercise Tolerance Tests

In older children and adolescents, a free-running exercise tolerance test is simple to perform and requires little equipment. One may also use a treadmill in a pulmonary function laboratory. A fall of >15% in FEV_1 and in peak expiratory flow rate (PEFR) or >25% in forced expiratory flow of 25–75% ($FEF_{25-75\%}$) is diagnostic of exercise-induced asthma.

Chemical Challenge Tests

Chemical challenges are valuable for the patients with presumptive asthma and/or chronic cough where baseline pulmonary function is normal and therapeutic trials with antiasthma medications are inconclusive. Patients with asthma have airways that are

Table 2
Laboratory Tests in Asthma[a]

Tests	*Possible abnormalities in asthma*	*Comments*
Complete blood count	Leukocytosis (occasionally)	Induced by infection, epinephrine, administration, "stress" (?)
	Eosinophilia (frequently)	Varies with medication, time of day, adrenal function; not necessarily related to "allergy" (often higher in "intrinsic" than "extrinsic" asthma)
Sputum examination	Eosinophils	In both "intrinsic" and "extrinsic" asthma
White or "clear" and small yellow plugs	Charcot-Leyden crystals	Derived from eosinophils
	Creola bodies	Clusters of epithelial cells
	Curschmann spirals	Threads of glycoprotein
Nasal smear	Eosinophils	Suggests probably concomitant nasal allergy
	Lymphocytes, PMNs, macrophages	Sometimes replace eosinophils in upper respiratory infections
	PMNs with ingested bacteria	Bacterial rhinitis or sinusitis
Serum tests	IgG IgA, IgM	Often normal; may be abnormal—various patterns seen
	IgE	Sometimes elevated in "allergic" asthma; markedly elevated in active bronchopulmonary aspergillosis, often normal
	Aspergillus-precipitating antibody	Suggestive, not diagnostic of bronchopulmonary aspergillosis
Sweat test	Normal in asthma	Cystic fibrosis and asthma can coexist
	Perform to rule out cystic fibrosis	
Chest X-ray	Hyperinflation, infiltrates, pneumomediastinum, pneumothorax	Indicated once in all patients with asthma; should be considered on hospitalization for asthma
Lung function tests	$\downarrow FEV_1$, $\downarrow FEV_{25-75\%}$, $\downarrow$ PEFR; $FEV_1/FVC \downarrow$	Useful for following course of disease, response to treatment
Response to bronchodilators	>15% improvement FEV_1, PEFR	Safest diagnostic test for asthma

Table 2 *(continued)*
Laboratory Tests in Asthma[a]

Tests	*Possible abnormalities in asthma*	*Comments*
Exercise tests	Decreased lung function after 6 min of exercise	Useful to diagnose asthma. Often abnormal when resting lung function is normal
	PEFR and FEV_1 > 15% ↓ $FEF_{25-75\%}$ > 25% ↓	
Methacholine inhalation test (mecholyl test); histamine inhalation test	20% Fall in lung function with dose tolerated by "normal" subjects	Should be performed by specialist only
Antigen inhalation test	20% Fall in lung function immediately after challenge; may cause delayed response 6–8 h later	Potentially dangerous; should be performed by specialist only
Allergy skin tests	Identifies allergic factors that **might** be causative factors	Test likely factors only—select by history
Serologic tests for IgE antibody (e.g., RAST)	Same significance as skin tests	More expensive than skin tests

[a]From ref. *3*.

overly sensitive to bronchoconstrictors. Methacholine and histamine challenges can be performed with standardized protocols that have high specificity and sensitivity for airway hyperresponsiveness and asthma. Patients inhale increasing concentrations of either of these chemical irritants according to a standardized protocol and perform spirometry after inhaling each concentration of the drug. The challenge is complete when FEV_1 has dropped 20% or more from baseline or when are one completes inhalation of a dosage of 25 mg/mL. A decline in FEV_1 of 20% indicates bronchial hyperresponsiveness. When this information is melded with a supporting clinical history, the diagnosis of asthma becomes likely. (On the other hand, a negative challenge usually excludes asthma.)

Distilled water inhalation, eucapneic hyperventilation of cold air, and hypertonic water inhalation are alternative challenge procedures. These are less well standardized than methacholine and exercise challenge. Inhalation challenge of specific antigens would seem to offer valuable diagnostic information regarding asthma triggers; however, in practice, antigen challenge has severe limitations. Antigen inhalation may produce bronchospasm in the laboratory, whereas only rhinitis occurs after natural inhalation. Also, late-phase reactions are common that may occur after the patient leaves the laboratory. **All bronchial challenge tests are potentially dangerous. They should only be performed by specialists who have had special training in their use.**

Nasal Cytology

These may be helpful in patient evaluation. The patient blows his/her nose or coughs into plastic wrap, the secretions are applied to a glass slide, heat fixed, and stained with Hansel's stain, an eosin-methylene blue combination that stains eosinophils distinctively. Alternatively, a tiny nasal brush or rhinoprobe device can be used to obtain a specimen from the wall of the nasal vault. The presence of >5–10% eosinophils indicates probable allergic inflammatory disease, but not necessarily asthma. The presence of large numbers of neutrophils and bacteria suggests infection. If the problem has been long-standing, the possibility of subacute or chronic sinusitis, which serves to aggravate bronchial hyperresponsiveness, should be considered.

Total Serum IgE

Total serum IgE determination may be helpful at times, approx 80% of children with allergen-induced asthma will have a total serum IgE > 2 SD deviations from the nonallergic population mean. More helpful, however, is evaluation of antigen-specific IgE.

Chest X-Rays

All patients with asthma should have chest X-rays at some time to rule out parenchymal disease, congenital anomaly, and foreign body. A chest X-ray should be considered for every patient admitted to a hospital with asthma, depending on the presentation and severity of asthma and any suspicion of complications, such as pneumonia and pneumothorax (Fig. 1). Chest X-ray findings in asthma may range from normal to hyperinflation with peribronchial interstitial infiltrate and atelectasis. In a 3-yr study of children hospitalized for asthma (1), the following abnormalities were seen: 76% had hyperinflation with increased bronchial markings; 20% had infiltrates, atelectasis, pneumonia, or a combination of the three; and 5.4% had pneumomediastinum often with infiltrates. Pneumothorax occurs rarely and did not occur in this study. Paranasal sinus X-rays also should be considered in patients with persistent nocturnal coughing and rhinorrhea.

Allergy Testing

Allergy testing (skin testing or serologic testing, such as radioallergosorbent testing or RAST) is indicated in patients in whom specific allergic factors are believed to be important. Testing is done with extracts of selective allergens based on history and known or potential allergen exposure. Asthma in children is frequently exacerbated by exposure to environmental allergens. In a given patient, the same antigen-specific IgE that can trigger inflammatory events in the airway can be detected in the skin. Antigen applied to the skin reacts with specific mast cell-bound antibody, which induces mediator release. Histamine will create local vasodilation with wheal and flare within 15 min, and a variety of chemotactic factors may create a delayed inflammatory response hours later. Although true positive skin tests indicate that a patient has antigen-specific IgE, it does not prove that exposure will create clinically significant disease. The predictive value of a positive skin test is enhanced if the reactivity is intense and occurs in conjunction with a positive provocative history.

As an alternative to allergen-specific skin tests, serum IgE against a specific antigen can be measured with serologic tests, such as the radioallergosorbent (RAST) test. In

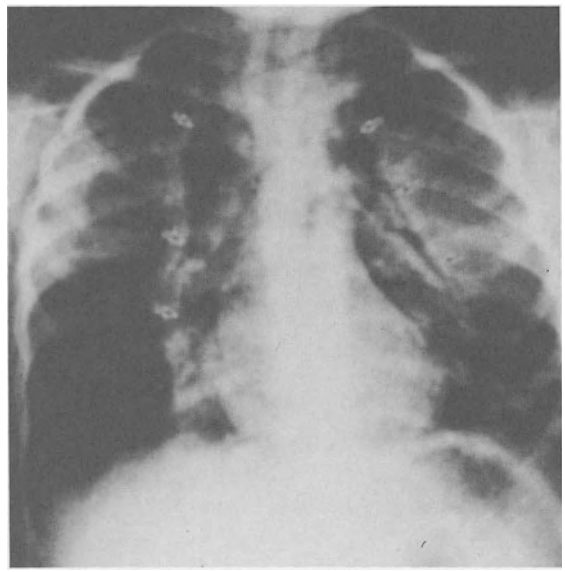

Fig. 1. Massive pneumomediastinum complicating asthma (from ref. *6*).

this procedure, antigens are coupled to an inert carrier, such as latex or cellulose, and mixed with the patient's serum, after which binding of antigen and patient's antibody is measured. In general, RAST is less sensitive and more expensive than skin testing. Its use may be needed in specific situations, such as when severe skin disease or dermatographism precludes skin testing, or when the subject is taking an agent, such as an antihistamine, that will suppress skin tests.

THERAPEUTIC CONSIDERATION

Philosophy of Management

A comprehensive approach to treatment of asthma requires an understanding of the disease, the manner in which patients present, and how the disease may affect physical and psychologic growth and development. The ultimate goals are to prevent disability and to minimize physical and psychological morbidity. These include facilitating social adjustment of the patient with the family, school, and community, including normal participation in recreational activities and sports. This adjustment is achieved in steps and should begin with early diagnosis and appropriate management of acute episodes. Irritant and allergic factors should be identified and eliminated from the patient's environment. Education of the patient's parents, the patient, or both to the long-term course of asthma, the management of exacerbations, and the importance of ongoing therapy to minimize acute exacerbations is an essential part of asthma treatment.

Achieving these goals requires time, knowledge, and experience. The demands on the physician will vary depending on the severity of the disease, the age of the patient, and the resources of the patient or family. The family physician or pediatrician who is willing to devote the time can care adequately for the patient with mild or moderate

Profile of a Child at Risk for Death from Asthma

- Teenage male
- Severe asthmatic, requiring daily medication to breathe
- Often from a minority group
- Noncompliant about taking daily, preventative medications
- Significant psychosocial problems in the family

asthma. Allergens and irritants that may be driving this disease should be investigated thoroughly in patients with all forms of asthma. However, the patient with moderate and severe asthma will benefit from referral to an allergist who has the knowledge and experience to modify therapy for special situations, educate the patient about asthma, follow the patient's progress, and act as a comanager with the primary care physician. Such a referral should help minimize acute attacks and the need for hospitalization or, when hospitalization is necessary, to reduce the length of hospital stay. A team approach that includes regular communication between the primary care physician and the specialist is essential for consistent and comprehensive long-term care.

Compliance by patient, family, or both is the keystone of any therapy. Compliance is influenced by many factors—the physicians's attitude, the family's and the patient's understanding of the disease, and peer pressure. It is in relation to compliance that psychological factors are of overwhelming importance. The attitude of the patient toward the disease is paramount in his or her willingness to follow the physician's recommendations. The patient's attitude toward asthma and the willingness to comply with recommendations reflect the parents' or peers' attitudes toward the disease. The physician's guidance can prevent overprotection or neglect by helping the family of a younger child cope with such aspects of asthma as the inconvenience of a medication schedule and environmental control. In older children, the physician should place the responsibility for taking medication on the patient. When medication is needed in school or at play, the patient should be permitted to take it privately without embarrassment. The physician should aid the patient in making decisions on such activities as sports, camping trips, traveling, and other activities when the patient is away from the home environment while ensuring appropriate control of asthma.

Finally, when a patient fails to comply, the physician should try to find out the reasons and should work out a reasonable solution, acceptable to the patient and/or the family. **Noncompliance in the face of severe disease, particularly in an adolescent, places him or her at great risk with regard to both morbidity from the disease and death.**

ENVIRONMENTAL CONTROL

Exposure to allergen and irritants at vulnerable times may significantly increase bronchial reactivity and adversely influence asthma control. The antigens most commonly implicated in chronic asthma are house dust mite, cockroaches, pet-derived antigenic proteins (with cat being the most common), and airborne molds and pollens. Although Murray reported on the beneficial influence of bedroom dust control measures in 1983, subsequent studies add to the information implicating dust mite antigen as a

Important Environmental Factors in Asthma

- Allergens
  - House dust mite
  - Cats and dogs
  - Cockroaches (inner-city)
  - Mold spores
- Chemical pollutants
  - Cigaret smoke
  - NO_2 (with poor ventilation)
  - Ozone (outside)

major factor in asthma. Certain environmental efforts are most successful for limiting mite antigen, but others that have been traditionally valued are not particularly helpful.

Dust mites are microscopic creatures that feed on human skin scales, require humidity >50%, and tend to seek darker environments. They are found in carpets, mattresses, and stuffed furniture in homes where the ambient climate is moderate and not too dry. They are not removed by traditional dusting and vacuuming. Encasing mattresses in airtight covers, washing pillows and bedding weekly in hot water (over 130°F), and removing carpeting, particularly if laid on concrete slab floors, will reduce house dust mite levels in the home. When carpets cannot be removed, acaricides, such as benzyl benzoate, and products that denature mite antigen, such as 3% tannic acid, sprayed on carpet and stuffed furniture, are helpful, as is reducing humidity to <50%. Most physicians concentrate efforts on education that relates to keeping the bedroom and family area as free as possible of house dust mite antigens.

It is unfortunate that pet removal can result in major improvement in asthma symptoms for some highly atopic patients, but that carrying out this removal is so difficult. Families are often unable to deal with the loss of a pet, putting asthma lower on the priority list than other psychosocial issues. If a pet to which a patient is sensitive cannot be removed from the home, certain temporizing measures are worthwhile: keeping the pet out of the bedroom, using tannic acid spray on carpets and furniture to denature pet antigen, or considering an electrostatic or HEPA filter. Studies that have shown that a weekly washing of cats reduces the amount of allergen deposited on carpet and furnishings are now controversial. Many pet antigens are tenacious molecules that travel easily and are difficult to eliminate from the home. The part-time indoor pet may produce the same antigen load as the full-time indoor pet, and it may take months after the pet is removed from the environment for residual allergen to decrease to nonproblematic levels. Also, the chronic inflammatory changes that occur with asthma often prevent patients and families from being able to appreciate improvement in asthma control with a brief period of pet avoidance.

Cockroach antigen is a problem primarily in the eastern and southern United States. Antigen concentration appears to be related in part to lower socioeconomic populations. Cockroach antigen may be more important than dust mite among this population. Attempts at environmental control include removing uncovered food sources, exterminating these insects, and repairing squalid and dilapidated conditions that support infestation.

Irritant exposure should also be limited to achieve best asthma control. Tobacco smoke exposure has been linked to asthma exacerbations, decreased lung growth, and age of onset of asthma. Therefore, smoking in the home should be forbidden. Wood stove heat has been linked to increased emergency room visits for asthma and should be avoided in favor of cleaner heating fuels. Atmospheric levels of ozone, SO_2, and NO_2 may be related to asthma exacerbations, although correlations are modest.

The amount of counseling that one offers concerning the environment depends largely on historical issues, level of allergy skin test relativity, and the ability of a family to make changes in their surroundings. The physician should offer firm counseling regarding environmental control if it is pertinent to a specific situation and then show flexibility when there are impasses. This approach is preferable to making an assumption that a family will not deal with avoidance and failing to provide appropriate information.

Home Peak Flow Monitoring

Another area of management is home peak flow monitoring, which is important in reviewing overall asthma control. Instruction in peak flow recording draws the patient or parent in as an active manager of his or her disease. Home peak flow monitoring is particularly suited to a subset of patients with asthma:

1. Children with fairly severe disease who may not appreciate early deterioration because they do not sense obstruction and hypoxemia;
2. Children whose parents are unclear about symptoms and would respond better to objective cues than to vague symptoms;
3. Children who are not communicative regarding symptoms; and
4. Children who need objective cues to spur compliance with medication regimens.

To increase the ease of monitoring, a color-coded system has evolved. A patient's chart contains colored forms where the "green" zone means 80–100% of best personal peak flow rate, "yellow" is 50–79%, and "red" is below 50%. The patient is instructed to exercise caution and use supplemental medication when in the yellow zone, and to notify the physician for further instructions when in the red zone. Some peak flow meters are color-coded, which aids the subject's assessment.

These nonpharmacologic management techniques should be part of an ongoing educational process that involves physician, patient, family, and other health educators, such as nurses and respiratory therapists. Education should begin with an explanation of asthma as an inflammatory disease, including an explanation of asthma trigger factors in and outside of the home, and should emphasize environmental control. It should stress the importance of monitoring pulmonary function. Pharmacologic intervention should be posed as an important element in the equation of optimal control, but not as the sole desirable intervention.

PHARMACOLOGIC MANAGEMENT

The goal of pharmacologic therapy is to improve pulmonary function and decrease lability in order to allow patients to have a "normal" lifestyle and to optimize lung growth. Drugs available in the United States are noted in Table 3. Rarely should patients

Table 3
Drugs for Management of Asthma in the United States at Current Writing[a]

Name	*Notes*
β agonist bronchodilating drugs	
Metaproterenol	2–3 h duration
Albuterol	4–6 h duration
Pirbuterol	4–6 h duration
Terbutaline	4–6 h duration
Bitolterol	4–6 h duration
Salmeterol	12 h duration
Nonsteroidal anti-inflammatory agents	
Cromolyn sodium (ampules and MDI)	Begin q.i.d.—reduce gradually to b.i.d. if possible
Nedocromil MDI	Begin q.i.d.—reduce gradually to b.i.d. if possible
Oral corticosteroids	
Prednisone (tablets/liquid)	Give as single morning dosage
Prednisolone (tablets/liquid)	Give as single morning dosage
Methyl prednisolone	Give as single morning dosage
Aerosolized steroids	
Beclomethasone	Administer every 8–12 h
Triamcinolone	Administer every 8–12 h
Flunisolide	Administer every 8–12 h
Fluticasone[b]	Administer every 12 h
Theophylline	
Various S.R. products available	Administer every 8–24 h Serum levels 5–15 μg/mL therapeutic
Other agents	
Anticholinergic (Ipratropium Bromide)	May increase albuterol bronchodilation
Methotrexate (Antimetabolite)	Experimental only, no pediatric trials performed
Troleandomycin (TAO) (Macrolide antibiotic)	Prolongs half-life of Methylprednisolone, no pediatric trials performed

[a]From ref. *3*.
[b]Introduced in the United States in 1996.

need to be satisfied with missing school or work time because of asthma, limiting physical activity, or sleeping poorly because of nocturnal exacerbations of their disease. This optimal lifestyle requires compliance with medication as well as avoidance of environmental trigger factors.

The National Heart, Lung, and Blood Institute has supported guidelines for the management of asthma that serve as an excellent foundation for treatment today. These guidelines stress the concept of inflammation in asthma and suggest that patients who require bronchodilator therapy more than twice a week for nonexercise-related asthma should have chronic anti-inflammatory therapy. A schematic view (Table 4) of a step approach to asthma care describes the ascent from simple bronchodilator to the use of nonsteroidal or steroidal anti-inflammatory medication depending on disease severity.

Table 4
Management of Chronic Asthma[a]

Classifications	*Assessment of lung function*	*Therapy*
Mild		
Asymptomatic	PEFR ≥ 80% of baseline	Children <5 y, nebulized cromolyn Children >5 y to adulthood, cromolyn or nedocromil
Symptomatic	20% Reduction in baseline	Children <5 y, nebulized or oral β-2 agonist Children >5 y to adulthood, inhaled β-2 agonist—2 puffs every 3–4 h if needed
Moderate		
Asymptomatic	60–80% of baseline	Children <5 y, nebulized or inhaled β-2 agonist t.i.d. or q.i.d. as needed and nebulized cromolyn Children > 5 y to adulthood, anti-inflammatory agents or theophylline
Symptomatic	Variation more than 30%	Oral corticosteroid burst plus nebulized or oral β-2 agonists
Severe		
Asymptomatic	<60% Baseline	Children <5 y, nebulized cromolyn and β-2 agonist up to q.i.d. Children >5 y to adulthood, inhaled β-2 agonist q.i.d., inhaled corticosteroids 2–6 puffs b.i.d. to q.i.d.
Symptomatic	50% Variation	Children, Prednisone 30–40 mg/d for 2 d, then taper to every other day dosage that stabilizes lung function Adults, 60 mg/d up to 1 wk, then taper

[a]From ref. *4*.

APPROACHES TO CARE

Treatment of Acute Asthma

An acute exacerbation of asthma poses an urgent medical problem as noted in Table 5. The best strategy for management is early recognition. Evaluation and treatment decrease worsening and abort further exacerbation and respiratory compromise. Early recognition by the patient and prompt communication between the patient and the health care provider are essential components of the process. They allow the physician to modify the individual patient's medication regimen and control his or her asthma more effectively.

The intensity of the acute attack and its outcome are influenced by a number of factors:

Table 5
Management of Acute Asthma[a]

Step	*Treatment*	*Assessment*
1. (After initial assessment) 0–40 min	Inhaled (nebulized) β-2 agonist twice, then β-2 agonist every 20 min for 1 h, systemic corticosteroids if no immediate response or if patient is currently on or recently has been on oral taper, oxygen 2–6 L/min consider sc epinephrine 0.3 cc (1:1000)	Peak flow, FEV_1, FVC, physical exam, O_2 sat if warranted
2. (FEV_1 > 50–70% predicted), 40–120 min	If not already initiated, administer systemic corticosteroids, continue treatment with topical or injected β-2 agonists 1–3 h if patient is improving (inhaled β-2 agonist, sc epinephrine, or 0.3 cc 1:1000)	Peak flow, FEV_1, FVC, physical exam
or		
(FEV_1 < 50% predicted) 40–120 min	Inhaled β-2 agonist hourly or continuous, begin IV corticosteroids (methylprednisolone 60–120 mg iv), oxygen 6 L/min or as required	Peak flow, FEV_1, continuous O_2 sat or ABG, physical exam (with severe symptoms, look for hypoxia, hypercarbia)
3. (FEV_1 > 70%) 120–180 min	Consider disposition: **for discharge home** Patient to continue frequent inhaled β-s agonist every 3–4 h as needed, and a short course of oral corticosteroids 40 mg po for 3–7 d, then either taper by 5 mg/d or give 10–20 mg po q.d. for 3–7 d; also include patient education on treatment plan and schedule medical followup	Home peak flow monitoring
or		
(FEV_1 < 70%) 120–180 min	For poor or incomplete response; **hospital admission;** consider iv aminophylline, respiratory support with O_2, continue inhaled β-2 agonist hourly (every 3 h) or continuously Disposition and appropriate followup must be determined on an individual basis; a patient with pertinent medical history, such as prolonged symptoms prior to visit, previous severe exacerbations, or pertinent psychosocial history, may require closer observation; in addition, any suggestion of deterioration throughout the course of treatment with increasing pCO_2 merits intensive care monitoring	FEV_1, FVC, continuous O_2 sat or ABG

[a]From ref. *4*.

1. The patient's age;
2. The duration of the episode;
3. A history of previous life-threatening asthma exacerbations requiring hospitalization, intubation, and intensive care, or complications secondary to hypoxia;
4. Recent and frequent emergency room visits; and
5. Either systemic corticosteroid usage or recent withdrawal from corticosteroids

Each patient should have available and be familiar with a "plan of action" to follow for acute asthma exacerbations. Peak flow measurements by the patient are important in this early assessment process and provide a more precise quantitation of airflow obstruction. The basic goal of treatment is to achieve a rapid reversal of airflow obstruction. The first line of therapy in this setting is repetitive inhalation of β-2 agonists. Poor or minimal response to β-2 adrenergic agonists is an indication for an emergent evaluation by medical personnel. Parents or patients should be instructed to administer a β agonist, for example albuterol, either by nebulizer at 0.1 mg/kg/dose (5 mg maximum) or two actuations of a metered does inhaler. If the patient's asthma is stable, these regimens can be repeated every 20 min up to three times as needed. If the initial response to treatment is good, based on PEFR ≥70% of the patient's personal best, then the β agonist should be continued every 3–4 h along with routine medications. If the patient responds only partially, he or she or the parents should contact their health care provider without further delay, who could initiate oral prednisone therapy at 1–2 mk/kg/dose and arrange for the patient to be seen in an emergency care setting. A β-2 agonist may be given up to every 2 h over the next 6 h.

When caring for a patient with acute asthma in the emergency room or clinic, the interaction should begin with a quickly obtained pertinent history and physical examination. It is important to ascertain relevant environmental exposures and infectious triggers, such as otitis and sinusitis.

Physical examination often reveals wheezing, accessory muscle use, and tachycardia. These findings are helpful to confirm the diagnosis of acute asthma; unfortunately, they do not reliably indicate the severity of the asthma episode. In the child under 3 yr, one may hear only coughing or signs of croup. Objective measurements include pulmonary functions, such as spirometry or peak expiratory flow rate. In severe asthma with lung function <50% of predicted normal and in young children with severe symptoms where peak flow cannot be obtained, one should attempt pulse oximetry or arterial blood gas measurements.

Early administration of oral or systemic corticosteroids should allow for more rapid improvement of pulmonary function. Close monitoring of the patient during treatment with repeated measures of lung function is essential for optimal management of the exacerbation and directions for changes in therapy. Supplemental oxygen should be administered to keep oxygen saturation above 95%. Nebulized albuterol should be administered at 0.15 mg/kg/dose every 20 min (maximum 5 mg/dose) for up to 1 h. Prednisone at a loading dose of 1–2 mg/kg should be administered orally. If the patient responds well, β agonist therapy should continue every 4 h until symptoms and peak flow measurements show that the patient has reached his or her normal baseline, but can be administered every 1–2 h if lung function continues to be poor until the response to prednisone is evident. The patient should continue prednisone therapy for at least 4–10 d to ensure adequate anti-inflammatory benefit. Although some physicians

Triggers of Acute Asthma in Children

- Viral infections
- Weather changes (especially in the fall and spring)
- Exercise
- Allergen exposure
- Irritant exposure (e.g., cigaret smoke)
- Emotional upset

will give the same total prednisone dose daily for 4 d, others will recommend a tapering dose over 4–10 d. Prednisone can be used as a single morning dose or can be divided during the day. However, the initial loading should be administered as a single dose. Patients with peak flow rates between 40 and 70% of baseline and O_2 saturation between 91 and 95% should be observed for several hours to assess response. The more severe the obstruction, the longer that the patient needs to be watched. If the patient continues to demonstrate severe symptoms, if poor peak flow rate continues (<40% of predicted), or if there is diminished O_2 saturation (<91%) in room air, hospitalization should be considered. Clinical findings, including the use of accessory muscles, presence of pulsus paradoxus, and increasing dyspnea or cyanosis, indicate need for hospitalization.

As an alternative to nebulizer therapy, epinephrine 1:1000 can be injected subcutaneously (.01 mL/kg up to 0.3 mL) repeated every 15–20 min for up to three treatments along with supplemental oxygen. This therapy is adequate, but involves the pain of injections and cardiovascular side effects of epinephrine that are often unpleasant.

Acute Severe Asthma in Children Requiring Hospitalization

If hospitalized because he or she responds poorly, the child should be managed in a facility where vital signs and overall condition can be monitored closely. The PEFR, O_2 saturation, and degree of dyspnea should be assessed frequently. Generally, if the peak flow is above 30% of predicted and the O_2 saturation is above 90% off of oxygen, the child with moderate dyspnea can be followed in an intermediate unit.

Children with more severe airway obstruction should be admitted to an intensive care unit and should have arterialized or arterial blood gases assessed. Supplemental oxygen should be continued and nebulized albuterol should be administered every 15–60 min as necessary with the administration of iv fluids. However, it is important not to overload the patient with fluids because of the danger of causing pulmonary edema. Further doses of systemic corticosteroids should be administered as oral prednisone or iv methylprednisolone or equivalent at 1–2 mg/kg/dose every 6 h. For the patient who is slow to respond, one may consider the use of iv aminophylline, although the benefit of this is now controversial in children. A loading dose of 6 mg/kg over 20 min followed by a continuous infusion of 0.9 mg/kg/h may be administered. The loading dose should be eliminated or reduced substantially if the patient has been maintained on therapeutic levels of theophylline pending a stat theophylline serum level. Theophylline serum concentration should be obtained 1.5 h after the loading dose, sev-

eral hours later, and then as indicated by the patient's course, and should be maintained at peak concentrations of <15 μg/mL.

If the patient fails to improve, and there are signs of respiratory failure, such as PEFR <25% of predicted, pCO_2 > 45 mmHg, and a falling pH value, continuous nebulization of a β-2 agonist should be considered. It should be noted that patients with severe asthma usually have carbon dioxide tensions <35 mm mercury. Intravenous terbutaline and mechanical ventilation should be considered in the child with rapidly rising pCO_2 or persistent hypercarbia. Antibiotics should be used only when there are signs of bacterial infection. Sedatives should be avoided, and food and fluid by mouth should be given only when the patient is no longer at risk of requiring mechanical ventilation.

As the child improves, preparation for hospital discharge should include a medication plan with emphasis on chronic medication and a short course of prednisone. The use of peak flow monitoring at home should be continued, and a followup clinic visit should be planned for shortly after discharge.

COMPLICATIONS OF SEVERE ASTHMA

Complications of asthma may be pulmonary or extrapulmonary. Pulmonary complications include:

1. Acute respiratory failure;
2. Atelectasis;
3. Pneumomediastinum and pneumothorax; and
4. Superimposed infections (pneumonia, emphysema).

Extrapulmonary complications include:

1. Vasopressin excess;
2. Hypokalemia;
3. Flaccid paralysis of an arm or leg;
4. Sudden alteration in theophylline metabolism with toxicity;
5. Cardiac arrhythmia;
6. Hypoxic brain damage and hypoxic seizures; and
7. Death.

Pulmonary and extrapulmonary factors may combine to cause acute respiratory failure, resulting in brain damage or death.

Pulmonary Complications

Respiratory Failure

Respiratory failure occurs in a small but significant number of patients admitted to the hospital with status asthmaticus. It often is the result of failure by the physician, patient, or family to recognize the severity of the patient's asthma. Clinical signs of overt respiratory failure include decreased or absent pulmonary breath sounds, severe intercostal retractions, pulsus paradoxus, use of accessory muscles of respiration, cyanosis with treatment with a final oxygen concentration (FiO_2) of 40%, reduced response to pain, poor skeletal muscle tone, and profuse diaphoresis. The use of accessory muscles of respiration, as previously noted, is one of the early signs of respiratory failure. These

signs indicate an extreme emergency and mandate immediate treatment **for acute** respiratory failure.

Arterial blood gas tension and pH must be monitored frequently in a distressed patient. Impending respiratory failure cannot be diagnosed from clinical signs alone. For example, a rise of $PaCO_2$ from 39 to 44 mmHg in 1 h in an exhausted patient who is receiving maximal therapy should be considered progressive respiratory failure and treated as discussed previously.

Atelectasis

Up to one-third of all hospitalized asthmatic children have had pulmonary complications, such as pneumonia and atelectasis, and 20% have had pulmonary infiltrates involving multiple lobes. Perihilar interstitial infiltrates will vary in severity from increased bronchovascular markings to shaggy, diffuse peribronchial viral pneumonia. Atelectasis of all or part of a lobe, the next most common complication, will occur in 10% of admissions. The right middle lobe is most frequently involved because of anatomic factors, e.g., the right main stem bronchus tends to twist with hyperinflation, resulting in its partial occlusion. Why right-middle lobe atelectasis develops more frequently in girls than in boys is not clear.

The treatment of atelectasis should be conservative. In most cases, it will resolve when the asthma is controlled. Respiratory therapy consisting of postural drainage and clapping as tolerated clinically is helpful. Intermittent positive pressure breathing (IPPB) therapy should be avoided, since it is likely to induce pneumomediastinum or pneumothorax. If atelectasis persists, the presence of a foreign body, an anatomic defect, or an obstructing peribronchial lymph node should be considered. Fiberoptic bronchoscopy may be useful if a foreign body is suspected.

Pneumomediastinum and Pneumothorax

In status asthmaticus, 5% of patients may develop extrapulmonary air. Shearing forces, from coughing and bronchospasm, superimposed on hyperinflation also related to atelectasis or pneumonia and possible structural weakness, cause air to rupture alveolar bases and to dissect along blood vessel sheaths (Fig. 2). These effects result in pulmonary interstitial emphysema. It manifests as a worsening clinical course associated with reduced venous return, cardiac output, and blood pressure. Air dissects along the great vessel sheaths to the mediastinum and pericardium and along the aorta to the intestinal wall or along the facial planes into the neck (Fig. 2). While this air remains under high pressure, asthma symptoms worsen and precardiac dullness disappears. Air may escape into the relatively low-pressure subcutaneous tissue of the neck and axilla, resulting in crepitant subcutaneous emphysema.

Rarely, pneumothorax complicates childhood asthma. It may be self-limited if small, or tension pneumothorax can occur that may severely compromise breathing. Bilateral pneumothorax can be the cause of sudden death in asthma. Tension pneumothorax that results from the rupture of a pleural bleb needs decompression with a chest tube and underwater suction (Fig. 3). A pneumothorax secondary to air rupturing through parietal pleura into the pleural space from a pneumomediastinum is less serious and may be treated conservatively. Often it will clear with treatment of the asthma.

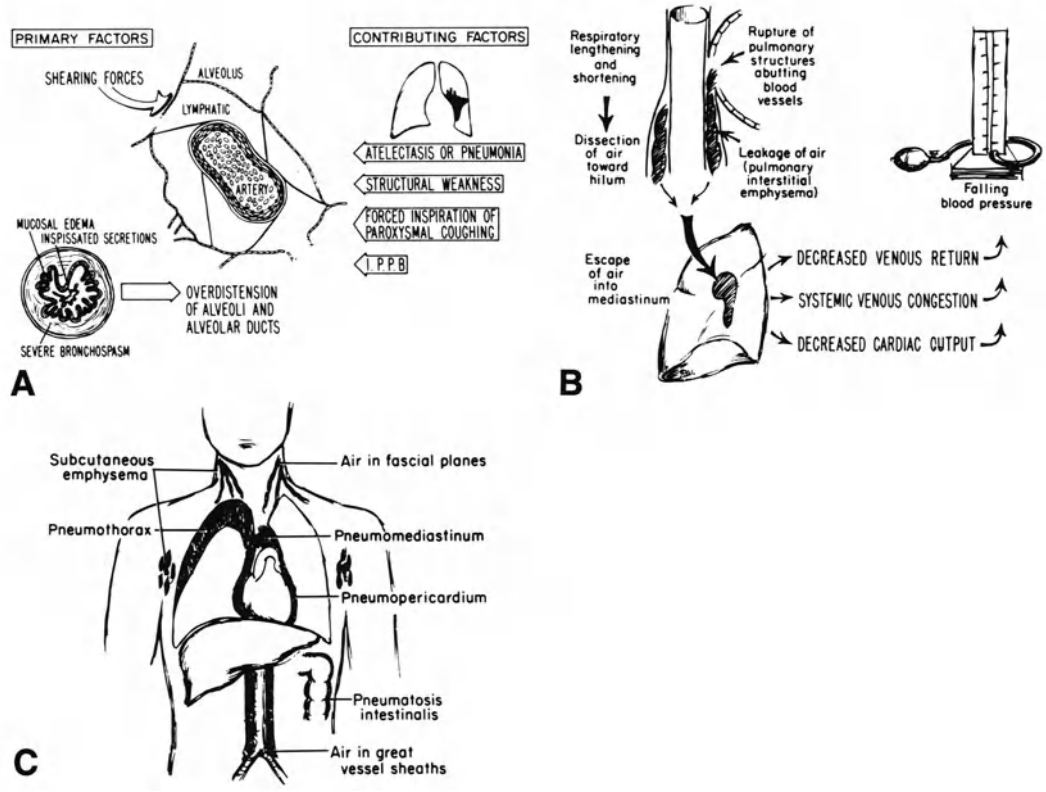

Fig. 2. Mechanism of pneumomediastinum in acute asthma (from ref. *6*).

Extrapulmonary Complications

Vasopressin Excess (Inappropriate ADH Secretion)

The release of ADH is regulated through such mechanisms as:

1. Pain, fear, and drugs acting on higher central nervous system centers;
2. Drops in arterial pressure;
3. Increases in plasma concentration (>280 mosM/L) of nondiffusible solute perfusing the hypothalamus; and
4. Decreases in stimulation of stretch receptors in the left atrium.

When filling of the left atrium is reduced, the vagus nerve stimulates the hypothalamus to secrete vasopressin. In severe asthma, vasopressin levels are elevated regardless of the serum sodium concentrations, apparently because of the effect of severe asthma on the pulmonary circulation. Vasopressin levels fall as the patient improves.

Criteria for the diagnosis of vasopressin excess are as follows:

1. Hyponatremia that is associated with plasma hypoosmolarity;
2. Continuing renal excretion of sodium in the presence of hyponatremia;
3. Absence of any evidence of dehydration;

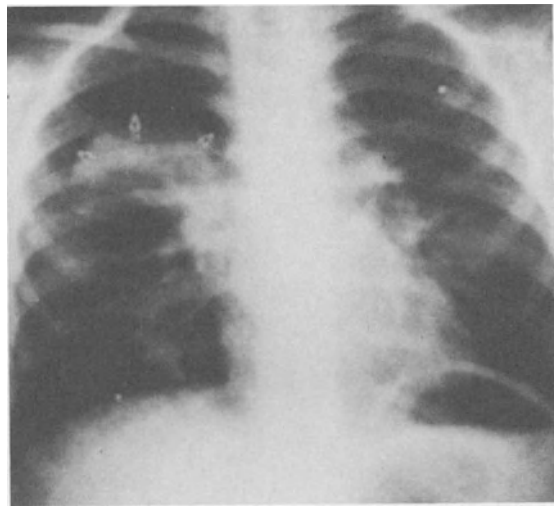

Fig. 3. Pneumothorax secondary to paroxysmal coughing in asthma (from ref. *6*).

4. Urinary osmolality value that is greater than plasma osmolality value; and
5. Normal kidney and adrenal function.

The treatment of excessive vasopressin involves three general principles. First, severe asthma must be corrected with appropriate therapy. Second, water intake and body weight, plasma electrolyte concentration and osmolarity, and urine volume and osmolality must be monitored closely; fluid intake should be restricted to the minimal amount compatible with control of asthma. Third, such complications as water intoxication with seizures should be treated with hypertonic saline and furosemide. Hypertonic saline and furosemide are rarely needed if the underlying asthma is treated successfully.

Hypokalemia

Aggressive dosing with both β agonists and corticosteroids has been associated with hypokalemia. This should be considered in the patient who requires prolonged intensive care. The presence of arrhythmia and muscle fatigue should certainly bring this possibility to mind.

Neuromyopathy

In 1974, Hopkins reported 10 children with flaccid paralysis after acute asthma severe enough to require hospitalization. The paralysis developed during the recovery phase from asthma, and all had been immunized for poliomyelitis. In all patients, paralysis was permanent, and involved one arm or one leg. To date, over 20 children with this syndrome from Australia, England, Sweden, and the United States have been reported in the medical literature, including one case of areflexic tetraplegia in a 10-yr-old girl. Severe myopathy appears to be an element in some, but not all of these pediatric cases as well as in several cases involving adults. Transient phrenic nerve paralysis also has been reported in status asthmaticus, possibly as a complication of assisted ventilation.

Cardiorespiratory Arrest with Brain Damage

Permanent hypoxic brain damage owing to cardiorespiratory arrest can be a complication of severe asthma and is particularly unfortunate because it is preventable with appropriate therapy. In the majority of these patients, it has been the result of the parent's or the physician's failure to recognize the severity of asthma and to institute appropriate therapy.

Death

Table 6 lists the causes of death associated with asthma in children. Most are potentially preventable, and can be avoided with appropriate education and treatment. Nevertheless, patients with a history of assisted ventilation and severe psychosocial dysfunction are at risk of death even when optimal care appears to be in place.

MANAGEMENT OF CHRONIC ASTHMA

It is important to recognize that chronic asthma may not be obvious in its presentation. Although there may be recurrent episodes of wheezing and shortness of breath, the presentation may be more subtle. Chronic cough may be the sole manifestation of asthma. When cough persists after each upper respiratory infection and when exercise tolerance diminishes markedly with each infection, asthma is a consideration. Patients may complain of exercise intolerance and become noticeably more winded than teammates during sports or may choose a sedentary lifestyle. The patient with a history of "recurrent bronchitis" or "pneumonia" may also have asthma. Both diagnoses are used as euphemisms to diminish anxiety, which actually prevents families and patients from dealing with the very manageable reality of asthma. Drugs useful in treatment of asthma are noted in Table 3.

For patients with intermittent episodes of mild bronchospasm who appear to be free of wheezing for days or weeks between problem times, intermittent therapy may be appropriate. One may choose an inhaled β agonist for children over 5 yr or an oral one for children under 5 yr of age. An alternative for the young child is a compressor-driven nebulizer, which can be used to provide β-2 agonists in saline as an aerosol that can be delivered by face mask.

Metered dose inhalers (MDIs) are effective for children above 4 yr of age and through adulthood. As the world moves away from Freon-containing propellants, more variations on "classic" MDIs are appearing, including breath-activated aerosol devices, dry powder devices, and dry powder capsules for puncture and inhalation.

Holding chambers devices (e.g., Inspirease®, Aerochamber®, Ace®) used with MDIs should be considered for two reasons: for lowering the age that MDIs are usable to about 4 yr by decreasing the difficulty of synchronizing actuation and inhalation, and also for increasing drug effect by improving lung deposition of drug. Some physicians report success with an inhaled corticosteroid and an aerochamber with face mask in small children. After each actuation, the mask is kept loosely over the child's face, and several inspirations and expirations are allowed before the next actuation. Usually these children continue to use nebulizer therapy with cromolyn and a β agonist several times daily.

With increasing incidence of symptoms, the patient requires a regular regimen. Obvious clues to this are frequent visits for emergency care and episodes that affect sleep and

Table 6
Causes of Death From Asthma[a]

Failure of physician or patient to appreciate severity
Lack of objective measurements
Lack of intensified therapy
Inappropriate therapy given
Too late owing to delay by patient of physician
Too little (e.g., low steroid dose or recent discontinuation)
Too much (e.g., β-agonists, theophylline, sedative abuse)
Progressive unresponsive asthma
Prolonged attack
Pulmonary complications
Infection (often undiagnosed)
Pneumothorax
Barotrauma
Aspirations of gastric contents
Malfunction of ventilator
Cardiac complications
Arrhythmias
Hypotension
Myocardial toxicity
Sudden cardiac arrest
Underlying cardiopulmonary disease
Hemodynamic
Hypovolemia, shock
Pulmonary edema

[a]From ref. 5.

school or work attendance. The use of home peak flow monitoring may well indicate that PEFR is chronically <80% of the patient's best baseline, that drops of 20–30% are taking place with some regularity, and/or that there is considerable variability between morning and evening peak flow. At the milder end of this spectrum, patients may do well with bronchodilator alone. However, as asthma becomes more severe, patients should be placed on chronic anti-inflammatory therapy. Many younger patients (under 5 yr) do well with cromolyn by nebulizer, whereas patients over 5 yr can use cromolyn by MDI and nedocromil if over 12 yr of age. Therapy usually begins with an ampule of cromolyn or two actuations of cromolyn or nedocromil on a regular 3 or 4 times/d basis, depending on the patient's particular need and age. Cromolyn and nedocromil can be tapered successfully to twice daily in many cases.

Nonsteroidal anti-inflammatory agents appear to prevent release of mediators from mast cells that induce acute bronchoconstriction and chronic inflammatory airway changes. In addition, these drugs may modulate the activity of neuropeptides and other inflammatory molecules that upregulate airway hyperresponsiveness. Cromolyn is useful as a maintenance, prophylactic agent for mild to moderate chronic asthma. In addition, cromolyn can be used intermittently to decrease exercise-induced asthma and to prevent antigen-induced episodes. Much of the data concerning cromolyn's anti-

inflammatory potential are based on studies using the no-longer available 20-mg capsule delivered by spinhaler device. Whether the currently available formulation by MDI (1 mg/actuation) provides equivalent action in the recommended dosage of 2 actuations is unclear. Cromolyn is administered by inhalation from the MDI or nebulizer. The nebulizer ampule contains 20 mg/2 mL and probably provides more therapeutic efficacy per dose than the recommended two actuations of the MDI.

Nedocromil is a pyranoquinoline that has specific anti-inflammatory effects on the airway. It has been shown to be effective in clinical trials of children and adults with chronic asthma. It appears to have prophylactic properties when used prior to antigen challenge as well as a variety of other challenges, including sulfur dioxide, cold air, and exercise. It appears to be similar to cromolyn in antiasthma potency. Whether its onset of action is faster, whether it is more potent, and whether it has steroid-sparing properties have not yet been determined. Approximately 13% of patients strenuously object to its taste and refuse to use it, whereas another subset found it unpleasant but tolerable. Nedocromil for asthma is currently available in the United States in MDI form.

If a 1-mo trial of a nonsteroidal anti-inflammatory drug is not beneficial, aerosolized corticosteroid therapy should be initiated. When the patient is stabilized with this, cromolyn or nedocromil can usually be discontinued. β agonist bronchodilators should be continued. If they continue to be needed several times a day and if nocturnal asthma continues to be a concern, the long-acting β agonist salmeterol can be added in hopes of stabilizing the patient's condition without needing a high dose of inhaled corticosteroid. If patients need a β agonist mainly in the day or mainly at night, salmeterol can be used just once a day, either in the morning or evening. There may be an advantage to avoiding 24 h a day β agonist therapy, which could possibly increase bronchial hyperresponsiveness.

Patients with severe asthma are those who have such problems as frequent symptoms affecting sleep and activity, as well as emergent visits and occasional hospitalizations. When untreated, their peak flow rates are markedly depressed and labile. These will require regular use of a β agonist and an aerosolized steroid, if the child is old enough to use an MDI. Short-acting β agonist by nebulizer or MDI can be used up to every 4 h. In patients who can use an MDI, salmeterol as a long-acting β drug administered at night may prevent nocturnal asthma and may simplify the β agonist regimen using albuterol as needed during the day. Children unable to use an MDI may respond to an inhaled steroid delivered from an MDI into an aerochamber with face mask. Others may require oral steroid therapy. If so, a short-acting drug, such as prednisone or methylprednisolone, used in the morning on alternate days will minimize steroid-induced adverse effects.

Theophylline is another bronchodilator that had great popularity in the United States until the late 1980s. It has lost its popularity for treating asthma because it is relatively difficult to use, safety and efficacy being related to serum levels, which must be monitored regularly for optimal risk: benefit ratio. Theophylline may be used as an adjunctive bronchodilator.

Essential points to know concerning theophylline are that:

1. In general, children over 1 yr and under 9 yr of age require a higher theophylline/kg dose than do older children, nonsmoking adolescents, or adults;

2. The ideal therapeutic range for maximizing effectiveness and decreasing adverse effects has been modified to 5–15 μg/mL in order to lessen risk of adverse effects; and
3. Diseases and drugs that affect the P450 cytochrome system in the liver can decrease theophylline clearance, and febrile infections, such as influenza can markedly elevate the serum theophylline levels.

Oral Corticosteroids

Corticosteroids are potent anti-inflammatory drugs that are available for asthma therapy in oral and inhalable formulations. Steroids are used in a variety of situations:

1. Short-term, systemic oral therapy, usually in high doses is essential for treating acute asthma exacerbations;
2. Short-term high-dose iv therapy is useful in status asthmaticus, although high-dose oral therapy can be sometimes used in these situations;
3. Inhaled topical corticosteroids are used as chronic maintenance therapy for moderate to severe chronic asthma; and
4. Low-dose oral daily or alternate morning therapy is used in severe asthma where inhaled steroids have not been adequate or where children are too young to use the aerosolized formulations.

For oral use, short half-life steroids, such as prednisone and methylprednisolone, are preferable, since they are less likely to affect pituitary–adrenal axis function than the longer-acting drugs.

Inhaled corticosteroids in usually recommended doses are unlikely to cause significant systemic adverse effects, although mild complications, such as throat irritation, hoarseness, or pharyngeal candidiasis (often asymptomatic), occur occasionally. As these agents have become more popular for treatment of asthma and as primary care doctors have been encouraged to become comfortable with prescribing them, there has been more discussion of potential risks, such as growth retardation, hypothalamic–pituitary–adrenal axis dysfunction, and possibly posterior subcapsular cataracts. With dosages that are usual for moderate disease, e.g., 400–800 μg/d beclomethasone equivalent, clinically significant adverse effects are very uncommon. Although higher dose therapy does increase the possibility of clinically significant evidence of systemic absorption, it is less than one would expect from oral steroid dosage for equivalent disease control.

Aerosolized agents currently available in the United States include beclomethasone diproprionate, triamcinolone acetonide, flunisolide, and fluticasone propionate. Their relative potency is difficult to assess. Some pharmacologists attempt to equate them on the basis of weight per actuation: beclomethasone 50 μg, triamcinolone 100 μg, flunisolide 250 μg. Since there are no direct comparative trials, these relationships are difficult to verify. More potent inhaled steroids for asthma include fluticasone, which has just been released, and budesonide, which is under investigation in the United States. Budesonide is being evaluated in a dry powder formulation to be delivered by a breath-actuated device as well as in a suspension for nebulizer delivery. The current absence in the United States of a nebulizer aerosol preparation poses a problem in caring for the very young child with severe chronic asthma. Some physicians have used

an aerochamber spacer with a face mask for children who need inhaled steroid and have had varying degrees of success with this delivery system.

Adding to difficulties in winning compliant behavior in the use of corticosteroids, the US Food and Drug Administration (FDA) has added labeling to topical steroid preparations regarding possible increased risk of disseminated varicella in children who use any systemic or topical preparation for asthma or rhinitis. The association between topical steroid use and such increased risk is speculative, whereas the association between infrequent oral steroid "bursts" for acute asthma and disseminated varicella is statistically real, but clinically remote. Now that varicella vaccine is available, children who require these medications who have not had clinical varicella should be immunized. The timing of this should be spaced as distantly as possible from the time of oral steroid therapy to maximize successful immunization, several months being optimal. The adequacy of immunizations can be assessed by measuring serum titers to varicella 1 mo following immunization. Many physicians now institute treatment with oral acyclovir when patients who are on or have recently been on oral prednisone and are not immune are exposed to varicella. Such therapy may also be used when patients who are on inhaled steroid develop varicella lesions.

Considering the potential risk of pituitary–adrenal axis suppression with regular use of oral or inhaled steroids, patients who require these medications and are scheduled for surgery or have experienced severe physical trauma are candidates for oral or parenteral corticosteroid replacement until the high-risk situation has passed.

Allergen Immunotherapy

Immunotherapy may be used as adjunctive therapy in patients who have an IgE-mediated component to asthma. Allergen immunotherapy has been shown to reduce the symptoms of asthma in double-blind studies with a variety of allergens, including house dust mite, cat dander, grass pollen, and *Alternaria*. Recent studies have also shown that allergen immunotherapy reduces the late pulmonary reaction to allergen in the lungs. Since immunotherapy modifies the allergic reaction to antigen, it is possible that its use might be most effective if administered early in the course of asthma. Since immunotherapy does carry risk of anaphylaxis, this approach to therapy should be considered in very specific situations and should be carried out by specifically trained physicians. It is very rarely indicated in children under the age of 5 yr.

PSYCHOSOCIAL ISSUES

Psychosocial issues inevitably influence chronic asthma management. For best results in caring for children, physicians must be listeners and educators. The therapeutic regimen should be simplified where possible to encourage compliance. Families should be counseled periodically on giving the child responsibility for his or her disease and its treatment without putting unrealistic expectations on those who are too young to assume it. Educational materials available through such groups as the Asthma and Allergy Foundation of America, Allergy and Asthma Network/Mothers of Asthmatics, and the American Lung Association can be helpful resources to parents and pediatric patients, as can support groups also identifiable through these national organizations.

GOALS

The goal of asthma therapy should be a normal lifestyle for the patient, as free of restrictions as possible. Usually, this can be achieved with appropriate therapy. Patients often benefit from home peak flow monitoring, objective data being helpful to the patient (and parents) and physician. Most disability from asthma is avoidable with appropriate monitoring and therapy.

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8 Asthma in Adults

Randy J. Horwitz, MD, PhD,
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CONTENTS

INTRODUCTION

The diagnosis and treatment of asthma account for the majority of allergy outpatient visits and virtually all inpatient referrals to the allergist. Both the overall prevalence of asthma in the United States and the mortality rate of the disease in certain sectors of the population are increasing. Although definitive contributors to this alarming rise in mortality have yet to be identified, some experts have implicated the increasing dependence on β agonists, the escalating levels of atmospheric pollutants, as well as the difficulties accessing appropriate health care facilities (especially in inner-city locales). A heightened awareness and thorough understanding of the disease by the primary care physician is essential in order to facilitate prompt diagnosis and early intervention.

From: *Allergic Diseases: Diagnosis and Treatment*
Edited by P. Lieberman and J. Anderson Humana Press Inc., Totowa, NJ

Increased knowledge of the pathophysiology of asthma has led to changes in our approach to the disease. Identification of inflammatory mechanisms responsible for the pathological changes observed in the asthmatic lung has led to the increased use of potent anti-inflammatory agents. The desire to attenuate severe side effects associated with systemic corticosteroids, as well as the development of improved drug delivery systems, has made the inhaled corticosteroid preparations a cornerstone of therapy. Recently, the availability of long-acting β agonists has resulted in a more balanced and less hectic pattern of bronchodilation, a feature particularly important in the treatment of nocturnal asthma.

The long-term care of the adult asthmatic patient constitutes a partnership between the patient and the health care provider. As such, the role of the physician as a health educator should not be underestimated. Care plans for asthma exacerbations should include detailed algorithms that provide patient-initiated interventions. This approach encourages the patient to be an active participant. Indeed, the need for hospitalization of an asthmatic patient commonly represents a failure in some aspect of the patient's health care plan, and thus mandates re-examination and a possible reformulation of the treatment plan by the patient and the physician.

This chapter will address the types of asthma commonly encountered in the primary care setting, help identify possible triggers for the disease, and summarize pertinent pathological and physiological features of asthma that have led to changes in treatment. In addition, we will discuss practical approaches to the diagnosis and management of asthma in the adult population.

DEFINITION OF ASTHMA

Asthma represents a complex syndrome of **airway inflammation**, **reversible airway obstruction**, and **bronchial hyperresponsiveness**. Although there are many different types of asthma that are commonly encountered in the primary care setting, these three characteristics are always present. There is considerable variation regarding which of the three features will predominate during an exacerbation, reflecting to some extent differences in the trigger, the chronicity of the attack, as well as genetic differences in the disease expression. Although there are many diagnostic methods of evaluating each of the three components of asthma, only a few are appropriate to the office setting and will be discussed below.

Airway obstruction is the entity responsible for most clinical manifestations of asthma, as well as the component of asthma most amenable to monitoring in the office or home setting. Monitoring of the peak expiratory flow rate (PEFR) using an easy-to-operate and inexpensive device can provide the patient and the clinician with a day-to-day assessment of airway obstruction. Such information can be used to detect trends in airway resistance that often herald asthmatic exacerbations. In addition, PEFR readings can be used as a guide for patient-initiated treatment interventions, utilizing physician-devised home health care plans. Spirometry, which enables the clinician to monitor accurately and easily other aspects of pulmonary function (including $FEV_{1.0}$ and FVC), is a necessary element of asthma management, and should be performed on every asthmatic patient. It is a technique that should be understood by any primary care physician whose practice involves asthmatic patients.

Key Features of Asthma

- Reversible (but not always completely so) obstructive lung disease.
- Bronchial hyperreactivity manifested by smooth muscle spasm to multiple stimuli.
- Inflammation of a unique type characterized by eosinophilia.
- May or may not have an allergic (IgE-mediated) component.

Bronchial hyperresponsiveness refers to an exaggerated bronchoconstrictor response to a variety of triggers. It is this component of asthma that is referred to as the "twitchiness" of the airways. Although the spectrum of triggers varies tremendously, accounting for a large degree of individual variation of the disease, the resulting bronchoconstriction is a common feature. This hyperreactive response of the bronchioles has been the subject of intensive study, with a variety of hypothesized mechanisms proposed, including airway inflammation, neural mechanisms, and intrinsic smooth muscle function alterations.

Airway inflammation is the newest entity to be accepted as a component of the asthmatic response. Although first proposed nearly 100 years ago, it is only in the past several decades that bronchoalveolar lavage and biopsy studies of asthmatic individuals demonstrated massive influx of inflammatory cells and their biochemical mediators during acute exacerbations. Autopsy studies of patients who died during status asthmaticus also corroborated these findings. Even persons with mild asthma display evidence of airway inflammation. Current therapy for chronic asthma reflects this key role of inflammation in the pathophysiology of the disease, as outlined below.

CLINICAL ASTHMA DESCRIPTORS

Clinicians have long sought to classify asthmatic patients into clinically relevant categories in order to facilitate treatment. There are only a few terms that have proven useful in the clinical setting. These are based on the severity of the disease, the frequency of exacerbations, and the degree of airway obstruction sustained. In addition, the recognition of several subtypes of asthma has led to unique diagnostic and therapeutic approaches.

Two broad categories of asthma often used by the allergist/immunologist are **extrinsic** and **intrinsic** asthma. These two categories are not mutually exclusive—many patients have features of both types and are often said to have mixed asthma. These categories refer mainly to the triggers and to the mechanisms involved in development of airway obstruction. We must remember that the end result of all types of asthma is similar, but the path chosen to arrive there differs.

Extrinsic (or allergic) asthma refers to inhaled allergen-driven cross linking of the IgE molecules present on airway mast cells, resulting in degranulation, mediator release, and the beginning of the inflammatory cascade described below. This type of asthma typically appears prior to the fourth decade of life and represents the most commonly encountered asthma in clinical practice. In order to diagnose extrinsic asthma, there must be: (1) a clear temporal relationship between exposure to the putative aeroallergen and the development of airway symptoms (either early phase, late phase, or both) to the inhaled trigger; and (2) demonstrable skin test reactivity to the inhaled trigger. A

seasonal variation in the frequency or severity of asthma symptoms provides the clue to the diagnosis of extrinsic asthma. An "educated" guess concerning the provocative trigger(s) can then be made based on a determination of regional patterns of pollenosis. For example, a patient living in the Midwest complaining of increased cough and dyspnea only during mid-August is probably experiencing ragweed sensitivity and reactivity. Skin testing will confirm the diagnosis. In most cases, the asthma symptoms will be accompanied by symptoms of allergic rhinitis (rhinorrhea, sneezing, ocular burning), making the diagnosis easier to recognize. An appreciation of the perennial nature of certain aeroallergens (e.g., dust mite) will ensure that the diagnosis is not missed.

Symptoms of **intrinsic asthma**, on the other hand, are not produced by traditional IgE-mediated reactions. Unlike extrinsic asthma, this type occurs in patients over the age of 40 and is typically triggered by upper respiratory infections, especially viral infections. Skin testing is usually negative, and there is no clear allergen exposure associated with asthma symptoms. Although the triggering mechanisms differ, both types of asthma result in a similar spectrum of symptoms. Thus, although the prophylactic therapy instituted for each type of asthma differs, the treatment of exacerbations is similar.

Occupational asthma refers to the development of asthma symptoms (changes in air flow) triggered by exposure to inhaled compounds in the workplace. It may or may not be mediated by IgE mechanisms. It is important to differentiate this type of asthma from exposure to irritants (chemicals, gases, metals, and so on), infectious agents, or even coincident adult-onset asthma unrelated to occupational exposure. This condition is often difficult to diagnose and, owing to the economic and social impact of the disease, of critical importance. It is estimated that occupational asthma represents approx 5% of all cases of asthma. Typical features of occupational asthma include a latency period of up to several years prior to onset of symptoms, worsening of symptoms shortly at the end of the shift or at night, and improvement in asthma symptoms on weekends. We generally recommend referral to a specialist for definitive testing and diagnosis, which often involves obtaining specific antibody titers, spirometry in the workplace setting, and bronchoprovocation with suspected agents. Some frequently noted causes of occupational asthma include toluene diisocyanate (TDI) in plastic workers, flour contaminants (mold or insect) among bakers, and plicatic acid from western red cedar wood dust observed among lumber workers in the northwestern United States.

Exercise-induced asthma, or more accurately, exercise-induced bronchospasm (EIB), is used to describe asthmatic symptoms present only in association with exercise. This differentiates it from exercise intolerance, a condition noted in many chronic asthmatics, that often prematurely terminates exercise sessions. This differentiation is important, since the clinician must be aware of the dual-phase (early and late) response that accompanies EIB and treat appropriately. Moreover, a unique feature of EIB is the lack of increased airway hyperresponsiveness or inflammation seen with other triggers of asthma. It is this fact that explains the unique treatment recommendations for EIB as compared to other types of asthma (discussed below). Bronchoconstriction in EIB asthma follows a characteristic pattern. During active exercise, the $FEV_{1.0}$ is relatively stable or even increased slightly, with no symptoms noted. Beginning at 5–15 minute after exercise, noteworthy drops in $FEV_{1.0}$ are observed, often at least 20–30%. Resolution occurs within 1 h, a late-phase response 4–6 hour later rarely occurs.

TRIGGERS OF ASTHMA

Viral upper respiratory infections have long been known to provoke asthma symptoms in susceptible individuals. The enhanced airway responsiveness and bronchial inflammation may persist for weeks beyond the acute respiratory illness. It has been suggested that viral infections occurring early in childhood may contribute to the pathogenesis or may even be the initiating event in the development of asthma. Among the respiratory viruses, respiratory syncytial virus (RSV) has been the subject of the most intense investigations regarding a viral role in provocation of asthma symptoms, particularly in young children. Among the older children and the adult asthmatic population, rhinoviruses have been shown to enhance airway responsiveness, promote the development of the late asthmatic response (LAR), and increase the airway inflammatory response to antigen. Interestingly, bacterial respiratory infections (other than sinusitis) have not been shown to lead to asthmatic exacerbations. It is likely that the complex patterns of cytokine elaboration in response to viral infections account for this difference, although other mechanisms, such as the production of virus-specific IgE antibodies, an enhancement of leukocyte inflammatory functions, or even viral-induced damage to airway epithelium, may also be important.

Bacterial infections of the paranasal sinuses also is known to occur in conjunction with asthmatic exacerbations. Although a direct causal relationship has been difficult to establish, numerous correlative studies have borne out this association. Many studies have supported the notion that vigorous treatment of underlying sinus disease (both medical and surgical) will ameliorate asthma symptoms and even improve pulmonary function. Even though most of these studies are uncontrolled clinical trials, or even anecdotal, most practitioners will aggressively treat sinus disease in all asthmatic patients. The mechanism of "sinusitis-triggered asthma" has yet to be determined, but once again, hypotheses abound. Some workers feel that a postnasal drip serves to transport inflammatory cells, bacteria, and biochemical mediators from the upper to the lower airway. A secondary bronchitis may then evolve, with resultant vagal nerve sensory fiber stimulation and reflex bronchospasm. Hematogeneous spread of cells and mediators have also been proposed as a means of "transforming" an upper respiratory infection to the lower airway. Neural mechanisms, such as the purported nasosinobronchial reflex involving trigeminal afferent and vagal efferent pathways, have also been put forth, although no compelling data have been published.

Allergens are thought to play a role in a majority of asthma cases in adults. Indeed, it is this hypothesis that led to the referral of asthmatic patients to the allergist in the first place. Atopic or extrinsic asthma is generally observed in the young adult through middle-aged population. As described previously, the etiologic mechanism for development of atopic asthma is postulated to be an IgE-mediated triggering of bronchial mucosal mast cells initiated by the binding of allergen. Respiratory symptoms may begin in minutes, as preformed mediators and cytokines are released. Lipid mediators, such as prostaglandins and leukotrienes, are produced by activation of arachidonic acid metabolism cascades. Clinically, these mediators produce an acute airflow obstruction or bronchospasm. This represents the early phase response (*see* Chapter 1). Many patients will recover from this early acute bronchospasm only to experience a second episode of bronchoconstriction 4–6 h after the initial antigen inhalation.

In certain patients, **exercise** induces asthma exacerbations, as noted above. The pathophysiology of this disorder is not well established, but some believe that it is triggered by changes in heat and water exchange occurring in the tracheobronchial tree during the passage of large volumes of air (as in vigorous exercise). The mechanism by which thermal fluxes cause bronchoconstriction is not clear. Support for this theory arises from studies indicating that EIB is tempered somewhat by exercising in environments with warm, moist air, such as heated swimming pools. This situation will lessen the temperature and humidity gradient between the bronchial tree and the outside environment. Conversely, exercise conducted in cold, dry air leads to an exacerbation of symptoms.

Gastroesophageal reflux (GER) accounts for 10–25% of all cases of chronic cough and is no doubt involved in many cases of nocturnal asthma. Repetitive stimulation of the distal esophagus, as well as reflux of gastric contents into the trachea and bronchial tree, is largely responsible for these symptoms. The fact that the esophagus and the bronchial tree share vagal innervation makes the mechanism of reflex bronchoconstriction more plausible as a hypothesis of GER-induced asthma. Patients who present with asthma symptoms that are related to position and/or postprandial symptoms warrant GER workup. Empiric trials of H2 blockers or proton-pump inhibitors may aid in diagnosis of this condition.

Emotional stress is acknowledged to contribute to airway responsiveness in some asthmatic individuals. However, there is no evidence to suggest that psychological factors provide the basis of the asthmatic condition.

Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDS) can provoke asthma exacerbations in susceptible individuals. Some studies estimate that up to 25% of all asthmatics may demonstrate such sensitivity, with increased prevalence in the presence of nasal polyposis, chronic rhinosinusitis, and steroid dependency. The pathogenic mechanism of aspirin reactivity is unclear. Crossreactivity among the various classes of NSAIDS is prominent. However, acetaminophen appears to be well tolerated in these patients. Some reports suggested that up to 20% of aspirin-sensitive patients also react to tartrazine (FDA Yellow Dye #5), a common dye found in food and drugs. However, these reports have not been substantiated.

Sulfiting agents, such as bisulfites and metabisulfates, can be an important precipitant or aggravator of asthma. Such chemicals are commonly used as antioxidants to prevent discoloration in food products and medications. Dried fruits and wine, as well as numerous items found on salad bars, are treated with sulfiting agents to preserve a fresh appearance. Usually, reactivity to sulfites is limited to severe, steroid-dependent asthmatics.

PATHOPHYSIOLOGY OF ASTHMA

The elucidation of the cascade of events leading to an asthmatic exacerbation has been aided by several innovations. Postmortem analyses of lung tissue from patients who have died in status asthmaticus have revealed numerous pathological changes. These include a marked infiltration of inflammatory cells, most notably the eosinophil. In addition, denudation of airway epithelium, collagen deposition beneath the basement membrane, and evidence of mast cell degranulation were seen.

The use of the flexible bronchoscope has enabled clinicians to obtain biopsy specimens as well as bronchoalveolar fluid (BAL) samples from the asthmatic lung. These studies often lend themselves to overinterpretation owing to the relatively small samples analyzed, yet they are presently the best sources of information available to the researcher. Molecules identified in the asthmatic airway by BAL techniques include inflammatory cytokines, arachidonic acid metabolites, and other biochemical mediators of the allergic and inflammatory cascades. Examinations of the pathology, cytology, and cytokine profile in affected airways have enabled the construction of a simplified scenario that aids in the understanding of asthma.

Inhalation of an allergen in an atopic asthmatic will result in filtration of large particulates in the nasal mucosa. Small (8 μ or less) diameter particles are able to pass into the larger bronchioles. On encountering mast cells with suitable IgE molecules on the surface, crosslinking occurs, followed by activation and degranulation. The T-cells resident in the airway (mainly $CD4^+$ cells) also react to the allergen, and are stimulated to secrete various cytokines, including IL-3, IL-4, and IL-5. These cytokines act as signals and attractants to many cells in the peripheral blood.

The processes involved in the egress of inflammatory cells from the periphery to the airway are complex and only now are being elucidated. The dilemma is that the body wants to attract only certain cell types to the nidus of inflammation, while reducing bystander trafficking. This seems to be accomplished via the use of specialized, selective adhesion molecules. These molecules are the adhesive tape utilized by nature in a variety of situations, including cell-to-cell communications, antigen binding (the immunoglobulins are a type of adhesion molecule), and cellular homing to a particular organ (helping T-cells migrate from the bone marrow to the thymus, for example). In the case of asthma, specialized receptor–ligand pairs form between inflammatory cells, such as eosinophils, and the endothelial cells that line the peripheral vessels. Three types of molecules, classified by their molecular structure, are involved in this, process: the **integrins**, the **selectins**, and the **immunoglobulin-like family**.

The function of these receptors is to control the egress of cellular traffic from the blood vessels to the airway. The specificity is such that only certain cells are allowed to pass into the airway following mast cell activation. Each of the three classes of receptors present on the leukocyte serves a unique function in the process of inflammatory cellular movement. The mechanism for the eosinophil migration is illustrated in Fig. 1. The first stage is that of "sticking and rolling." The eosinophil sticks to activated vascular endothelium by virtue of the selectin molecules. This adherence is not tight, and, owing to the shear forces of vascular flow, the eosinophil rolls along the endothelial barrier. Further activation of the inflammatory leukocyte by extravascular stimuli as it rolls leads to its tight adherence to the endothelial cells. This is then followed by diapedesis (from the Greek, "to pass through"), which is the extrusion of the cell through the endothelial intracellular space. This process of transendothelial migration is mediated by the actions of the integrins and the immunoglobulin-like receptors. These three classes of molecules thus work in concert to allow selectively only those cells with activated counter receptors to pass from the bloodstream into the airway, where they can carry out their effector functions.

To summarize the complex cellular events occurring in an asthmatic exacerbation, it is best to consider the scenario as an invasion. Inhalation of an allergen represents the

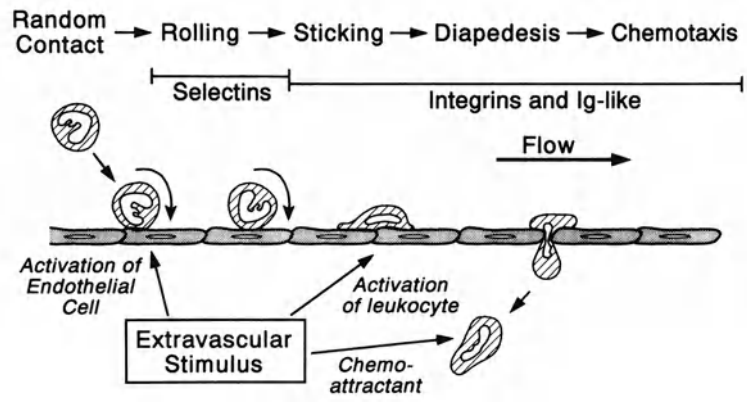

Fig. 1. Eosinophil migration to the airway in asthma. Schematic diagram of the transendothelial migration of the eosinophil in response to an extravascular stimulus in the airway. The involvement of the various adhesion molecules at each stage of the process is illustrated at the top of the figure. From ref. *1*, with permission.

enemy assault. The mast cells, already armed with IgE (the radar system for nonself, molecules) on their surfaces, is the body's first line of defense. They are instantly excited and triggered by the binding of antigen. Within minutes, thousands of preformed granules are discharged in retaliation. Histamine and tryptase are released, which causes bronchoconstriction (with the physiological role being to inhibit further entry to the airway?), and increased vascular permeability and mucus production (to dilute and trap the offending allergen?). This mast cell response constitutes the early phase asthmatic response. Although it produces clinical asthma symptoms, the body is in no way finished repelling the assault of the allergen. Over the next several hours, the body begins assembling troops and reinforcements for what is to become the late-phase response. Diverse cell types are summoned to the area, in what is surely an exaggerated response to an inhaled antigen. Specific T-cells (T_H2 type) send out the cytokine signal that an allergen has breached the host defense barrier and has invaded the respiratory system. These cytokines serve to alert and stimulate B-cells, eosinophils, and even the endothelial cells that line blood vessels. Each responds to the crisis in its own manner, with B-cells increasing IgE production, eosinophils increasing their bone marrow production rate and priming for mediator release, and endothelial cells producing a selective barrier to cellular migration to the airway by virtue of increased receptor expression. *De novo* synthesis of lipid mediators (the prostaglandins and leukotrienes) also begins. These compounds are arachidonic acid metabolites produced from integral cell membrane lipids on mast cell activation. The leukotrienes are very potent bronchoconstrictors and also function as chemotactic agents, summoning neutrophils and eosinophils to the area.

The overall effect of an asthmatic exacerbation is an early response using preformed mast cell granule contents, a lag phase during which inflammatory cells are mobilized, and finally a late-phase response wherein inflammatory cells and newly synthesized mediators act on the airway (Fig. 2). Although a well-orchestrated immune response to a trigger may seem appropriate in the case of an infectious agent, such avid defense mechanisms are superfluous in the case of an allergen or chemical irritant. Indeed, it is

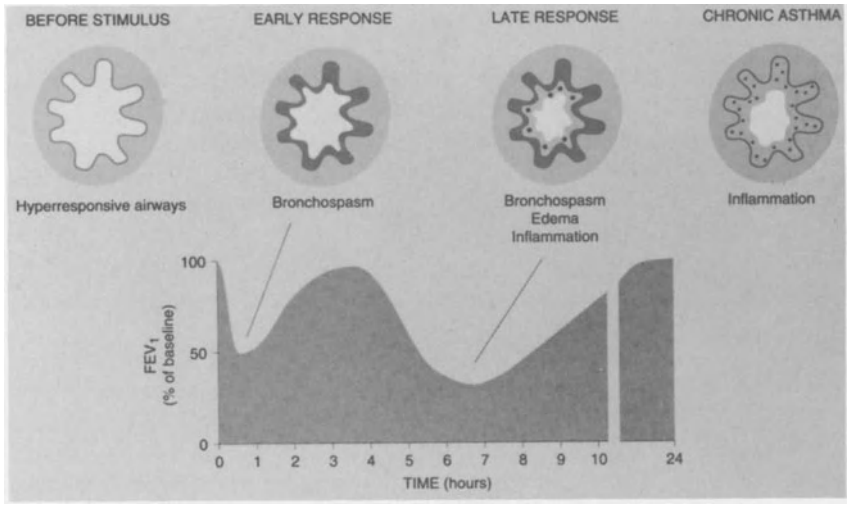

Fig. 2. The early and late phase asthmatic response. Changes in bronchial airflow, as demonstrated by a decline in $FEV_{1.0}$, correspond to anatomical changes in the airway, including increased inflammatory cell deposition, increased airway edema, and bronchospasm. From ref. *2*, with permission.

this exaggerated response to a seemingly innocuous invader that characterizes the asthmatic airway.

DIAGNOSIS OF ASTHMA

The presentation of asthma may be as characteristic as episodic bouts of dyspnea and wheezing when the patient is in the proximity of cats, or as vague as a nocturnal cough in the absence of an identifiable trigger. The first directive as a clinician is to include or exclude asthma as a diagnosis. This is best accomplished by way of a complete history, physical examination, and certain laboratory investigations.

Historical features consistent with the diagnosis of asthma reflect the heterogeneous etiologies of the disease. A thorough clinical history can be a major aid in ascertaining whether asthma is present and provide some clues regarding the triggers involved (Fig. 3). The presence of a history of atopy is helpful, since approx 50% of asthmatics older than 30 yr of age are allergic. The presence of associated allergic conditions, such as chronic sinusitis, atopic dermatitis, or allergic rhinitis, may also aid in the diagnosis of asthma. A family history of asthma or atopy also favors the diagnosis, but definitive patterns of inheritance have not yet been elucidated. The episodic nature of true asthma also reveals itself during the medical history. It is helpful to try to identify patterns in the occurrence of asthma symptoms. For example, many asthmatics report symptoms in the early morning hours, often disrupting normal sleep patterns. These symptoms usually correlate with low endogenous corticosteroid production, which reaches a nadir in the diurnal cycle between 4 and 6 AM. Identification of a precipitant of an asthmatic exacerbation is of great help in the diagnosis and treatment of the disease. Common triggers, such as viral illnesses, environmental allergen exposure, or even certain drugs, may be reported (detailed above). Once an identifiable and reproducible trigger has been noted, provocative testing may often be performed.

Key Features of Diagnosis of Asthma

- The history is the most important element and may be characterized by complaints of wheeze, dyspnea, or cough (or any combination thereof).
- The absence of physical findings does not rule out the disease.
- Lung function tests are essential, and in the absence of detectable abnormalities on random testing, a challenge test (exercise or methacholine) may be indicated.
- The presence of peripheral eosinophilia is characteristic and the degree of eosinophilia may correlate with the severity of symptoms.

Presenting symptoms may include any combination of dyspnea, wheezing, or coughing. Indeed, cough-variant asthma has been well described. Usually, the patient will be asymptomatic at the time of the clinic visit, necessitating some degree of recollection, along with detailed questioning. Clarification of such descriptors as "shortness of breath" or "chest pain" is often necessary. In addition, the degree of exertion necessary to elicit symptoms should be noted in detail. Detailed descriptions of a "typical" attack, including prodromal symptoms, time-course of acute and resolution, phases, and response to medications, are useful.

The usefulness of the physical examination in the diagnosis of asthma is a subject of much debate. The examination is meaningful in the assessment of the patient in the midst of an exacerbation. However, most asthmatics are quiescent between exacerbations, or at least asymptomatic in the practitioner's office. There are no pathognomonic physical findings seen in asthma—acute or chronic. In the asymptomatic patient, the examination of the chest will be completely normal. Occasionally, evidence of hyperinflation is noted in chronic asthmatics, but this finding is not restricted to asthma. The nasal examination often reveals turbinate edema, rhinitis, or even polyps, all consistent with atopic disease. In the midst of an exacerbation, airflow obstruction may or may not produce audible wheezing, depending on the level of airflow. A prolonged expiratory phase is also often noted in the midst of an asthmatic exacerbation.

The most important laboratory test to perform on the suspected asthmatic patient is the measurement of lung function, either with spirometry (most accurate) or peak expiratory flow rate, both before and after bronchodilator treatment. The presence of airflow obstruction that is responsive to bronchodilator treatment, combined with a compatible history, provides the diagnosis of asthma (Fig. 4). The absence of airway obstruction mandates peak flow monitoring, a technique akin to "home spirometry." The peak flow meter (described below) measures peak expiratory flow rates and should be used by the patient at least twice per day in order to establish a baseline airflow rate. Use of the peak flow meter during symptomatic periods, as well as bronchodilator responsiveness, will aid in the determination of airflow obstruction. Variations in AM and PM peak flow rates of >20% usually indicate airway hyperresponsiveness. The absence of airflow obstruction as determined by spirometry or PEFR leads to the bronchoprovocation test, a measure of airway hyperresponsiveness. This test consists of inhalant provocation with increasing concentrations of either methacholine or histamine. Changes in pulmonary function are assessed after each incremental increase in agonist dose, usually using spirometry. In the case of EIB, exercise challenge (usually treadmill) is used in place of chemical provocation. A decrease of 20% in the baseline $FEV_{1.0}$ following challenge is

Historical Cues in Workup of the Asthmatic Patient

Symptoms experienced (e.g., wheezing, coughing, chest tightness, dyspnea)
Frequency of symptoms (twice daily, daily, weekly, monthly, and so forth)
Severity of symptoms (hospitalizations, emergency room visits, number of workdays missed
Temporal symptoms (i.e., perennial vs seasonal)
Timing of symptoms (e.g., nocturnal symptoms)
Exercise intolerance
Known precipitants (i.e., strong odors, specific locales, temperature or weather changes)
Family history of asthma or allergic disease
Childhood asthma or allergies
Previous therapies and efficacy

Fig. 3. Historical cues in the workup of the asthmatic patient. These areas of questioning are useful in the diagnosis and care of asthmatic patients, and should be considered when conducting clinical interviews.

consistent with the diagnosis of asthma. Results of these tests are expressed as the cumulative dosage or lowest dosage of test agonist resulting in this decline in baseline $FEV_{1.0}$.

Other laboratory tests that may provide a clue to the diagnosis or etiology of asthma include CBC with eosinophil count, chest radiograph (will rule out other causes of obstruction), sinus radiograph (usually a Water's view is an appropriate screen), and aeroallergen skin testing (best performed by a specialist). The use of sophisticated esophageal manometry or pH testing for gastroesophageal reflux disease is usually postponed until an empiric trial of anti reflux measures and medications has been implemented.

TREATMENT OF ASTHMA IN ADULTS

Prior to the initiation of a treatment plan for any ailment, it is first necessary to establish realistic goals of therapy. In asthma, we week to decrease the total number of exacerbations, while striving to ensure that the periods between exacerbations are symptom-free. In addition, it is desirable to maintain a high quality of life; one in which asthma does not present an obstacle to an individual's goals or interests. Thus, one aims to prevent EIB symptoms in a would-be athlete and to eliminate dyspnea in an allergic farmer at harvest times.

Asthma is a chronic disease and, as with all chronic conditions, one must consider adherence issues when designing a care plan. The most efficacious regimen available is useless if the patient finds it impossible to comply with a difficult, time-consuming medication schedule. Likewise, if the patient does not perceive an immediate clinical benefit from the medications prescribed, their continued usage is jeopardized. This is often the case with the use of inhaled corticosteroid preparations. Although β-agonists provide prompt, although temporary relief of bronchoconstriction, corticosteroids offer no perceived immediate benefit. The introduction of long-acting inhaled β-agonists will no doubt complicate this problem. It is at this point that the benefits of patient education become obvious. Once the patient appreciates the role of each prescribed medication in the total care of his or her condition, he or she becomes an active partner in the health

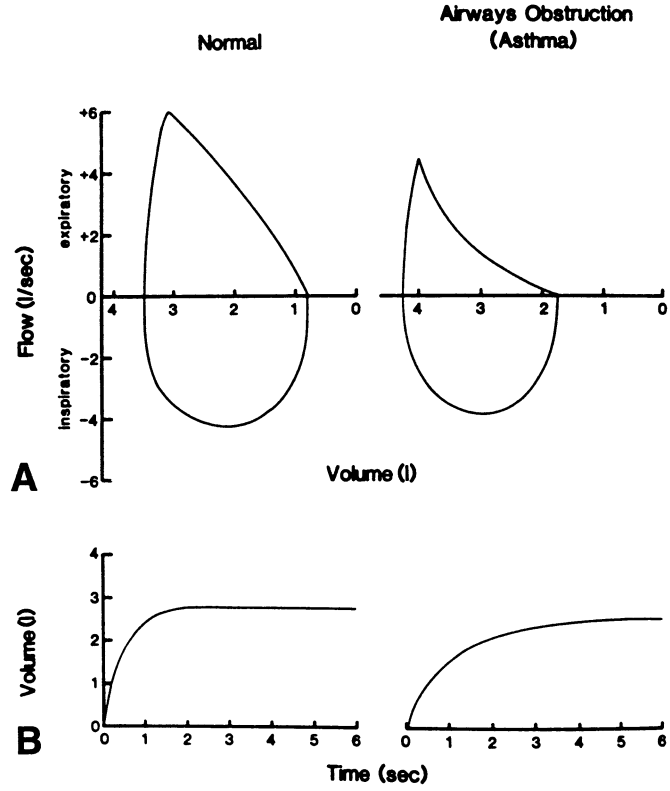

Fig. 4. Airflow mechanics in asthmatic patients. Representative flow-volume loops (**A**) and volume-time curves (**B**) in normal and asthmatic patients. Concavity of the expiratory phase of the loop is indicative of airflow obstruction, as is the prolonged time required to achieve total FVC. From ref. *3*, with permission.

care team and is able to share his or her insights and perceptions with the practitioner. The increased role of the patient in asthma management will benefit both the patient and the practitioner in the long term.

GUIDELINES FOR THE MANAGEMENT OF CHRONIC ASTHMA

There is a distinct difference between the treatment of an acute asthmatic exacerbation and the management of an asthmatic individual. The treatment of the acute exacerbation is a rather routine application of basic pharmacological principles and is often described algorithmically. It is essential that all primary care physicians recognize and promptly act to treat these exacerbations, or to refer the patient to the nearest emergency department for appropriate care. We will discuss the principles of acute care of asthma below. Proper long-term management of the asthmatic patient, however, embodies the art of medicine. The challenge is to:

1. Devise an easy-to-follow regimen that will serve to protect the patient from exacerbations;
2. Educate the patient to recognize trends in the development of the asthmatic exacerbation, using peak flow meters, for example; and

Principles of Treatment of Chronic Asthma

- A care plan is dependent on the classification of the severity of the illness.
- Pharmacologic measures should be accompanied by environmental control and also immunotherapy when indicated.
- Control of inflammation is essential.
- Constant encouragement, education, and assessment of compliance are necessary.
- Complicating factors such as sinusitis, rhinitis, and gastroesophageal reflux, should be controlled.

3. Provide a "care plan" whereby the patient can initiate appropriate therapeutic intervention at the earliest sign of an exacerbation, and thus assume some responsibility for his or her care.

In this way, the patient will gain experience and eventually self-assurance in dealing with his or her asthma. Prior to even considering the management of the asthmatic individual, however, the clinician must gain an appreciation of the severity of the patient's disease and the impact that asthma has on the patient's life.

Effective long-term management of the patient with chronic asthma requires the primary care physician to establish a close working relationship with the patient. This enables the physician to understand the extent of the disease, the role that the disease plays in the patient's life, as well as encouraging the patient to take an active role in his or her own health care. Although we will describe an algorithm for the care of asthmatic patients, the clinician is warned that this is just a guideline. As with all regimens, no rules are written in stone—clinical finesse is achieved by recognizing the limitations of each available therapy and by formulating a plan that creatively regards these limits.

An assessment of the severity of asthma is an essential prerequisite to the formulation of a care plan. Many consensus committees have produced detailed algorithms for management of asthma; however, none agree on the assessment of symptomology. In formulating a care plan for your patients, several factors must be considered.

Frequency of exacerbations is an essential indicator used to assess overall disease severity as well as the clinical efficacy of treatment regimens. The definition of an exacerbation differs among patients, so a working definition must be established, such as "a prolonged (i.e., several days) period of continued reliance on a β-2 agonist, with either limited resolution of symptoms or markedly decreased duration of bronchodilation with each use." Although there are no universally accepted definitions, a significant increase in severity or frequency of symptoms, with or without the increased use of therapeutics, might be useful indicators of disease activity and the effectiveness of treatment.

Frequency of asthma symptoms provides another important measure of asthma severity. An asthma "symptom" differs from an exacerbation mainly in duration. When asthma symptoms, such as cough, wheezing, or dyspnea, persist for extended periods, producing an overall change from a patient's baseline, this constitutes an exacerbation. If, however, the patient notes slight shortness of breath once per day, which promptly resolves following β-2 agonist treatment, then this simply represents a "symptom."

Severity of asthma symptoms is perhaps the most difficult factor to assess, yet it may be the most important. A patient who reports only two asthma exacerbations per

Clinical characteristics	Mild asthma	Moderate asthma	Severe asthma
Frequency of symptoms	<2 episodes per week	>2 times per week	Continuous symptoms
Nocturnal symptoms	Rare or absent	Frequent	Frequent
Baseline $FEV_{1\,0}$	Normal	60–80% predicted	<60% predicted
Typical exacerbation duration	<24 h	Several Days	Up to 7 d
Emergency room visits	Rare	Occasional	Occasional-frequent

Fig. 5. Characteristics of mild, moderate, and severe asthma. These clinical categories are useful guidelines for the initial classification of asthmatic patients into relevant treatment categories. Although few patients fit precisely into one category, a pattern of predominant symptoms should dictate the appropriate grouping. Adapted from ref. *4*.

year may initially be regarded as a mild asthmatic. If these two attacks required prolonged hospitalizations along with mechanical ventilation, then your assessment of the seriousness of his or her disease would change. Common indicators of asthma severity used by specialists include frequency of nocturnal symptoms, need for hospitalization, need for emergency room visits, number of corticosteroid bursts required over the past several months, and frequency of β agonist use over a 24-h period. There is considerable subjectivity on the part of the clinician regarding severity of asthma symptoms. The contribution of each aforementioned indicator must be weighed on an individual basis for each patient. The National Asthma Education Program has developed guidelines for the assessment and classification of asthmatic patients (Fig. 5), which we have modified somewhat.

THE CARE PLAN

The "care plan," or algorithmic treatment plan, for the asthmatic patient is a primary tool in disease management. The use of this device can streamline patient care and provide a means to assess the status of asthma, as well as allow the patient to participate directly in the care of his or her asthma. When designed appropriately, the care plan should be flexible enough to allow for some variation by the individual patient, yet firm enough to dictate criteria for seeking outside help.

A key component of the care plan is the peak flow meter. When properly used, this meter provides an objective measure of airflow obstruction available to the patient at home. The PEFR correlates well with the $FEV_{1.0}$ measured by spirometry. All new asthmatic patients should be given a peak flow meter and instructions on its use. In addition, baseline values should be obtained both mornings and evenings, before and after β agonist use (if appropriate) during a 2-wk asymptomatic period (or period of no exacerbations). This will both establish the normal diurnal values for that patient and provide rough estimates of bronchodilator responsiveness. These values should be recorded in a permanent diary, along with any pertinent symptoms, and will provide a baseline reference point from which future changes in treatment can be based. The patient may then utilize the peak flow meter during periods of symptomatic exacerbation to obtain objective data on airflow obstruction. Indeed, most therapeutic interventions are based on changes in the peak flow values (in the context of symptoms). The NAEP has established guidelines for PEFR monitoring to be used as an aid in recognizing early changes

All clear/green zone:	80–100% of predicted or personal best PEFR; no asthma symptoms are present; no alterations in medication regimen are required.
Caution/yellow zone:	50–80% of predicated or personal best PEFR; may be predictive of an impending acute exacerbation. Patient should institute care plan and follow up with physician should symptoms fail to improve within 24 h. Frequent or regular declines into yellow zone mandates re-evaluation of maintenance therapy.
Medical alert/red zone:	PEFR below 50% of predicted or personal best; often signifies impending severe exacerbation. Patient should utilize b agonist and immediately contact physician.

Fig. 6. The zone system for peak flow monitoring. PEFR's provide a convenient way to monitor airway obstruction in the home setting. Evaluation of peak flows is done by comparing current performance to a patient's best (asymptomatic) reading, or a predicted value obtained from a nomogram. Three categories of performance are defined for the test, each with an associated treatment plan. Adapted from ref. *4*.

in airway obstruction (Fig. 6). The patient should be warned, however, that it is the trend in the PEFR values, rather than the individual readings, that mandates action.

MAINTENANCE THERAPY OF CHRONIC ASTHMA

Decisions regarding initial therapy for chronic asthma are made based on the clinical criteria we have discussed, and modified based on clinical efficacy. We have provided several suggested regimens that may serve as a starting point for chronic asthma therapy (Fig. 7). Mild asthmatics are often well controlled with β-2 agonist used on an "as-needed" basis. These patients are generally asymptomatic, with normal $FEV_{1.0}$ values between attacks. We do instruct these patients to perform baseline PEFR at the time of diagnosis to establish personal baselines and note diurnal variations, if any. We also ask that, prior to use of the bronchodilators, repeat PEFR be obtained to provide an idea of the severity of the airflow obstruction. Should there be a change in the degree of obstruction or the frequency of bronchodilator use over the course of a week, the patient is to notify us by phone. Greater than 6 puffs/d or the appearance of nocturnal symptoms warrants further investigation and the possible addition of an anti-inflammatory medication.

Moderate asthma is characterized by the presence of frequent nocturnal symptoms, symptoms occurring on three or more days per week, or a baseline $FEV_{1.0}$ between 60 and 80% of predicted. This degree of asthma usually requires the addition of an anti-inflammatory preparation to the regimen. The goal is to attempt to normalize both the symptom profile and the objective pulmonary function tests. The inhaled corticosteroids represent a major boon to the treatment of asthma and should be used aggressively. Using these agents, we are able to provide anti-inflammatory effects directly to the bronchial tree with negligible adverse side effects seen with oral corticosteroids.

There are presently three families of inhaled corticosteroid preparations available in the United State (Fig. 8). Thus far, there is no compelling evidence that any one medica-

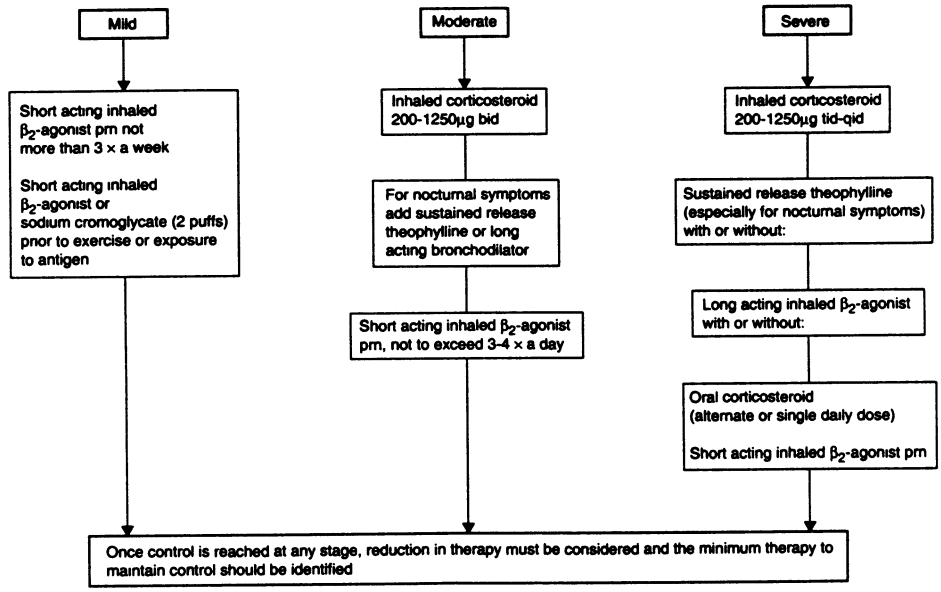

Fig. 7. The management of chronic asthma: maintenance regimens. A simple algorithm for initiation of treatment in patients with mild, moderate, or severe asthma. These recommendations may then be modified based on clinical responses. We routinely increase the inhaled corticosteroid dosages to higher levels if needed (*see text*). From ref. *5*, adapted from ref. *4*, with permission.

tion is more potent on a molar basis. We usually begin treatment with no less than 320 μg of inhaled steroid/d, which corresponds to eight puffs of beclomethasone. We always attempt to simplify dosing regimens to twice per day—although there is some evidence relating frequent dosing of inhaled steroid preparations to increased efficacy, there was also a marked decrease in compliance. We feel that twice-a-day dosing increases adherence while remaining efficacious. In order to decrease the frequency of the local side effects associated with inhaled corticosteroids, we always recommend the use of a spacer device. In addition, we implore our patients to rinse their mouths with water after the inhalations are completed to reduce the oropharyngeal deposition of steroids, which may contribute to oral candidiasis, dysphonia, or nonspecific cough. We follow spirometry, PEFRs, and symptom diaries with each office visit (commonly every 3–4 mo), and make adjustments in the dosages as needed. It is worth remembering that it will often require up to 4 wk of regular use of inhaled corticosteroids before maximal efficacy is achieved. We increase dosages up to a maximum of about 3000 μg of inhaled steroid/d. Beyond this level, patient compliance (owing to time, as well as financial constraints) diminishes, and often systemic steroids are required. Dosage recommendations for the individual inhaled corticosteroid preparations are presented in Fig. 8.

When an asthma exacerbation occurs in a previously well-controlled patient, the use of systemic corticosteroids should not be delayed. A slow decline in the daily PEFR measurements without an increase in symptoms may often be corrected with increases in inhaled steroid doses. However, with a worsening of symptoms, the benefit of initiation of systemic corticosteroids far outweighs the risks. We generally use doses of

Corticosteroid	Dosage form (μg/actuation)		Dosage recommendation (μg/day)		
	MDI	DPI	low dosage[b]	moderate dosage[c]	high dosage[d]
Beclomethasone dipropionate	42, 50,[a] 100,[a] 200,[a] 250[a]	100,[a] 200,[a] 400[a]	200-600	600-1000	>1000
Budesonide	50,[a] 200[a]	100,[a] 200,[a] 400[a]	200-800	800-1600	>1600
Flunisolide	250		500-1000	1000-2000	>2000
Fluticasone propionate	25,[a] 50,[a] 125,[a] 250[a]	50,[a] 100,[a] 250,[a] 500[a]	100-750	750-1500	>1500
Triamcinolone acetonide	100		400-800	800-1600	>1600

a Availability varies between markets; these forms are not currently available in the US.

b Indicated when symptoms interfere with daily activities; use of a β-agonist inhaler 2 to 4 times/day; small variations in peak expiratory flow rate (PEFR).

c Indicated when more severe symptoms >1 to 2 times/week; exacerbations affecting sleep and activity levels; occasional emergency care; use of a β-agonist >4 times/day.

d Indicated when frequent/continual symptoms, or night-time or early awakenings; use of a β-agonist inhaler >4 times/day; FEV_1 and PEFR 60 to 85% of predicted; PEFR variability >30%.

Abbreviations: DPI = dry powder inhaler; MDI = metered dose inhaler.

Fig. 8. Dosage recommendations for inhaled corticosteroids in the treatment of asthma. Only three of the five inhaled corticosteroids listed are available in the United States, and only in the strengths noted. We generally begin with a "low" dose and titrate upward until a clinical response is seen. There are no significant differences in potency between the preparations when compared on a molar basis. From ref. *5*, adapted from ref. *4*, with permission.

0.5–1.0 mg/kg of prednisone daily for 1 wk (usually 10 mg tid), followed by 10 mg once/d for the second week, after which the drug is discontinued. Prednisone bursts of <1 wk duration usually do not require tapering.

Recent studies have determined that optimal nocturnal asthma control may be achieved by the administration of one of the prednisone doses between 3 and 5 PM, which we normally recommend. Although the long-term effects of steroids are well appreciated, the clinician should be aware of short-term adverse effects. Nervousness, difficulty sleeping, increased appetite, mild hyperglycemia, dependent edema, and dyspepsia are commonly noted, and are reversible following discontinuation of the medication.

Patients who require frequent oral prednisone bursts (one or more per month) should be placed on extended oral corticosteroid regimens, with very slow tapers. It is common to taper a "brittle" asthmatic over a 6–8 wk period, with weekly prednisone decreases of as little as 2.5 mg/wk. Rarely are patients who are steroid-dependent or even steroid-resistant encountered. These patients are difficult to manage and often benefit from specialized medical regimens. The care of such patients is best left to the specialist.

In patients with moderate asthma, the addition of a long-acting inhaled β-2 agonist is often preferable to frequent dosing with shorter-acting preparations. The use of a long-acting agent, such as salmeterol, provides stable maintenance of the bronchodilated state without peaks or valleys, or rebound bronchial hyperreactivity frequently seen with short-acting medications. In addition, salmeterol, when given at bedtime, will often ameliorate nocturnal asthma symptoms, allowing for uninterrupted sleep (i.e., no need to redose the bronchodilator in the middle of the night). Some studies even suggest that salmeterol inhibits early and late-phase allergic reactions (at least in the laboratory setting). Generally, we consider using salmeterol in patients with moderate or severe asthma who use six or more inhalations of a short-acting bronchodilator per day or who have frequent nocturnal symptoms. Approximately 5–10% of our patients note a persistent cough while using the medication. The use of a spacer device is of some help, but in a proportion of these patients, the cough persists, and they are forced to discontinue the medication.

Environmental control measures may provide considerable improvement in those asthma patients with demonstrable skin test reactivity to aeroallergens. Such interventions may provide symptomatic palliation in up to 85% of all asthmatics. Outdoor allergens, such as pollens, weeds, grasses, and molds, are rather ubiquitous, and thus amenable only to avoidance as a control measure. Air conditioning should be employed during peak periods of allergen exposure, both in the home and the automobile. Exposure to aeroallergens should be limited, and particulate masks may be used in forced exposure situations, such as job-related exposures. Indoor provocateurs, such as animal, cockroach, and dust mite allergens, are more amenable to control measures. Of the animal allergens, cat allergen appears to be the most tenacious and potent. Elimination of the cat from the household is the most efficacious therapy. However, even then there is a lag period of up to 6 m prior to significant reduction of the allergen in the air. If elimination is not a viable option, then certainly elimination from the bedroom, frequent (weekly) baths, and prompt washing following contact with the animal are advised.

Allergy to house dust mite antigens is a major cause of perennial allergy symptoms, and no doubt contributes to the development and exacerbation of asthma. Here, too, environmental interventions have been shown to attenuate the level of mite antigens in the household, and thus reduce symptoms. Elimination of carpeting and draperies in the bedroom, weekly hot water washing of bed linens, and the encasement of mattress and pillows in mite-impermeable covers all are useful. A nonatopic individual should vacuum the home at least weekly, and the asthmatic patient should avoid freshly vacuumed rooms for at least 2 h to allow the airborne allergens sufficient time to settle. Maintenance of household humidity levels at or below 40% on a year-round level, and judicious use of acaricides will also decrease the mite population.

High concentrations of cockroach allergens are found primarily in inner-city environs and in warmer climates. The elimination of roaches from infested dwellings is difficult at best and nearly impossible in multifamily residences. However, a decrease in exposure to cockroach allergens will likely aid in the management of asthma in susceptible individuals.

Immunotherapy remains a viable option in select patients with atopy and asthma. The presence of a seasonal variation in asthma symptoms combined with appropriate skin test sensitivities warrants consideration of immunotherapy as a treatment modality. Double-blinded controlled studies have demonstrated a reduction in asthma symptoms with a variety of aeroallergen extracts, including house dust mite, grass pollen, *Alternaria*, and cat dander. The time and commitment required for a prolonged course of immunotherapy generally restrict patient selection to those individuals with moderate to severe asthma who have unavoidable allergen exposure (e.g., working outdoors) and require excessive β agonist support during their allergy season.

ADJUNCT THERAPIES IN CHRONIC ASTHMA

Theophylline, nonsteroidal anti-inflammatory agents (cromolyn and nedocromil), and anticholinergics are also used in the treatment of chronic asthma. These medications are used in concert with the inhaled corticosteroids and β agonists, or in certain cases on their own. Here we will consider each of them individually. Further discussion of these drugs may be found in Chapters 18–20.

Theophylline is one of the oldest agents used in the treatment of asthma. Theophylline-containing compounds exhibit bronchodilator activity, in addition to producing some augmentation of respiratory muscle contractility. Mild anti-inflammatory activity has also been reported by some researchers. The usefulness of this preparation is tempered by its relatively narrow therapeutic window. The advent of the slow release, once-per-day preparations decreases the frequency of adverse effects from supratherapeutic dosing. The initiation of asthma therapy with theophylline is more common in childhood asthma and, when effective, is often continued through adulthood. Theophylline is typically added to an adult's regimen when breakthrough symptoms are occurring despite high doses of inhaled corticosteroid preparations and long-acting β agonists, or in patients with refractory nocturnal asthma. In addition, there are some patients who are unable to tolerate inhaled corticosteroids or high doses of β agonist—these patients may benefit from theophylline therapy.

When dosing theophylline preparations (either 12-h or 24-h preparations), it is best to titrate up from a low dose, with changes made no sooner than every 3 d. Serum theophylline levels may be checked 3 d after a change in dosage and should be drawn approx 8 h after a dose. We use a target serum theophylline level of 5–15 μg/ml, which should provide clinical efficacy without gastrointestinal side effects (nausea or vomiting). When devising theophylline dosing regimens, care should be given to conditions that increase (smoking, concomitant use of phenytoin) or decrease (concomitant use of cimetidine, allopurinol, or erythromycin) its metabolism.

The inhaled nonsteroidal anti-inflammatory compounds presently available include cromolyn sodium and nedocromil sodium. These agents are effective in the prophylactic, rather than therapeutic, management of asthma. These drugs are used more frequently in the pediatric population, perhaps owing to their high safety profile. They are also useful in two conditions in the adult population: EIB (discussed below) and bronchospasm caused by a known allergen. In addition, we have used the compounds in patients who are unable to tolerate inhaled corticosteroids and theophylline. The compounds are effective when used immediately prior to exercise or allergen exposure (e.g., before entering a home containing a cat) in susceptible individuals, and have been shown to attenuate the early and late-phase allergic responses. The mechanism of action has not been fully elucidated, but at least some effect is mediated by a modulation of inflammatory cell function. We do not routinely initiate therapy with these agents in adults with "typical" asthma. Rather, we prefer to use the inhaled corticosteroids as first-line agents, and use the nonsteroidal anti-inflammatory drugs in a more limited fashion.

Anticholinergic therapy is more commonly used in the treatment of chronic bronchitis than asthma. At present, the only approved use of the available anticholinergic drug, ipatroprium bromide, is in conjunction with a β agonist in acute asthma. The structure of ipatroprium decreases absorption, and anticholinergic side effects are minimal.

TREATMENT OF ACUTE ASTHMATIC EXACERBATIONS

Despite compulsive attention to warning signs and rigid adherence to treatment plans, some asthmatic patients will eventually develop an acute exacerbation. Just as care plans must be individualized, so must the strategy for dealing with the acute exacerbation. A guideline for initial management of the acute exacerbation is shown in Fig. 9.

Key Features in the Management of the Acute Attack

- Objective measurements (peak flow, oximetry, blood gases) are needed to assess initial plan and the decision concerning whether to admit.
- Cornerstone of therapy is repeated nebulization of a β-2 agonist.
- Early institution of systemic corticosteroid therapy and corticosteroid therapy on discharge may be imperative.
- The decision to admit to the hospital should be made within 4 hr of entrance into the emergency department.

A gradual decline in airflow, as evidenced by increased asthma symptoms or increased bronchodilator use, demands adherence to a peak flow monitoring regimen, both before and after bronchodilator treatment. Peak flow values <80% of a patient's best value constitute activation of the care plan, as documented above. Repeat peak flow measurements taken 15–20 min following bronchodilator treatment should return the patient to the green zone (80–100% range). If this is indeed the case, we advise patients to continue regular bronchodilator use for 24–48 h. If peak flows are sustained at 80–100% of best, then the patient may return his or her pre-β agonist usage. In addition, if the patient is normally on an inhaled corticosteroid preparation, we instruct him or her to increase the dose by 50% for a 10-d period. For example, the patient taking beclomethasone 4 puffs twice/d will now take 6 puffs twice/d for 10 d. This increase is initiated regardless of the bronchodilator response. The additional steroid may provide added anti-inflammatory coverage to attenuate any airway hyperresponsiveness that might be associated with the asthmatic trigger, or as a result of the increased β-agonist use.

Failure to achieve at least 80% of maximal peak flow after bronchodilator therapy is termed an incomplete response, and suggests a more severe exacerbation. We routinely begin an oral corticosteroid regimen, usually over a 2-wk period. Thoughtful questioning of the patient may uncover an underlying etiology of the attack, such as concurrent sinusitis, which may be amenable to antibiotic treatment.

A peak flow reading that fails to increase beyond 50% of baseline after bronchodilator treatment is termed a "poor response" and warrants action on the part of the patient. The severe acute asthma exacerbation requires prompt medical evaluation and treatment. The recommendation to come to the clinic or emergency department for therapy indicates that the patient has already proceeded with some type of prearranged plan of action, as documented above, and has failed to respond sufficiently. We recommend that the patient contact a physician by phone at this point, but should not delay seeking treatment if discomfort and asthma symptoms are progressing rapidly.

Initial evaluation in the clinic or the emergency room is similar. Objective measurements of pulmonary function are essential and should not be overlooked. This is particularly true in those patients in whom the diagnosis of asthma is uncertain. Objective examination and data can often help differentiate common masqueraders of asthma, such as vocal cord dysfunction. In addition, the use of a spirometer or peak flow meter provides information regarding the degree of responsiveness to bronchodilator therapy, allowing monitoring for therapeutic efficacy. One would not diagnose and treat a myocar-

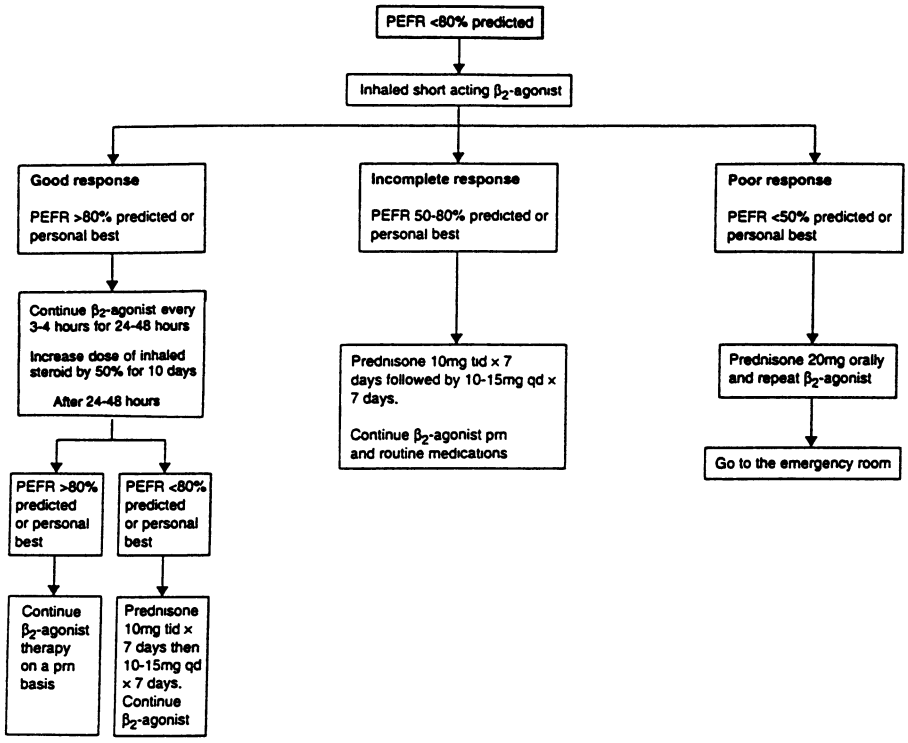

Fig. 9. Protocol for the early treatment of exacerbations in chronic asthma. This algorithm is useful for the outpatient management of exacerbations in patients with chronic asthma. These are often manifested by declines in PEFR or increases in asthma symptoms. The most common treatment error in caring for exacerbations is undertreatment—either with too low a steroid dose or an inadequate treatment duration. From ref. *5*, adapted from ref. *4*, with permission.

dial infarction without an electrocardiogram, so one should not treat asthma without a measurement of airflow. The use of pulse oximetry is a useful and noninvasive measure of gas exchange, and its use often precludes the need for a blood gas determination.

Of course, the clinician should always seek to establish and treat precipitants of the acute asthma attack. Recent upper respiratory tract infection, contagion contact, or allergen exposure is readily identified and may be amenable to treatment. Commonly, the cause of the attack remains elusive. In addition to treating the exacerbation and its trigger, the clinician must recall those risk factors that portend a prolonged and often turbulent recovery (Fig. 10). For example, severe asthma exacerbations with lengthy recovery periods are seen in older patients, patients with a history of previous life-threatening exacerbations, and patients who have recently tapered their corticosteroids.

The cornerstone of treatment of an acute asthma attack is the frequent use of β-2 agonist preparations. The delivery system is not as critical as the dosage used. However, nebulized treatments seem more effective in patients in whom metered dose inhaler (MDI) treatments at home proved ineffective, or in patients incapable of coordinating the breathing patterns and breath-holding required for adequate MDI drug deposition. We usually begin treatments with 2–4 puffs of albuterol/MDI or a nebulizer treatment every 20 min as needed for up to 1 h. Intermittent monitoring of $FEV_{1.0}$ or PEFR aids in

Red Flags: Historical Features Demanding Attention During Acute Asthma Attacks

Age >60
Prolonged duration of current episode (>14 d)
History of life-threatening asthma exacerbation (including intubation, ICU monitoring)
History of recent or frequent ED visits
History of recent corticosteroid taper
Presently using corticosteroids
Presently using β blockers
Lack of available medications at home (indicating noncompliance)
Comorbid cardiopulmonary conditions

Fig. 10. Risk factors for severe asthmatic exacerbations. This table lists some of the criteria to consider when treating an acute asthmatic exacerbation. Any combination of these factors may contribute to produce a severe or even life-threatening situation. Patients with these characteristics deserve special attention and prompt care during periods of acute illness.

gaging therapeutic efficacy. Complete recovery of $FEV_{1.0}$ or PEFR along with resolution of wheezing and/or shortness of breath is grounds for discharge, with close medical followup, plus increases in inhaled steroids (50% dose increase for 7–10 d), or β agonists (every 4–6 h while awake for several days) at least until followup. Of course, any treatable precipitants should be addressed.

A lack of complete improvement warrants systemic steroid administration, along with hourly nebulized β-2 agonist treatments. Subcutaneous epinephrine may also be efficacious if the β agonist is not resulting in adequate reversal of symptoms. Four hours following initiation of treatment, a decision should be made regarding admission. Certainly, if the response is not complete—that is, $FEV_{1.0}$ or PEFR < 70% predicted along with persistent wheezing—then the patient should be admitted, with continuation of systemic corticosteroids. This decision is individualized for each patient, and is largely dependent on a previous history of severe exacerbations, steroid use at the time of attack, adequacy of home conditions, and so on (Fig. 10). A good response to the hourly nebulizer treatments and systemic corticosteroids often leads to discharge, with a 10–14 d burst of oral corticosteroids, a regular β agonist regimen, and close medical followup.

ASTHMA IN PREGNANCY

Asthma in pregnancy is a topic worthy of special consideration. It is estimated that 5–10% of all pregnancies are complicated by asthma. In fact, asthma is one of the most common illnesses that occurs during pregnancy in the United States. Asthma may first present during pregnancy or existing asthma may worsen during pregnancy. There is no way to predict the effect of an individual pregnancy on a patient's asthma—there is an equal probability that a pregnancy will worsen, improve, or have no effect on preexisting asthma. What is clear, however, is that untreated asthma can harm both the mother and the fetus. Pregnant patients with asthma should be reassured that, with properly controlled asthma, their pregnancy should present little or no increased risk to themselves or their fetuses.

As with all asthma (and especially allergic asthma), avoidance of provocative triggers is a key to nonpharmacologic control. We do not recommend routine skin testing of pregnant patients because of the risk associated with adverse reactions and their treatment. Avoidance procedures for known allergens, including severe limitations on outdoor exposures to aeroallergens during peak periods and house dust mite reduction protocols, should be instituted in susceptible individuals.

The choices of pharmacotherapy for asthma in pregnancy are somewhat limited owing to the paucity of clinical experience with many medications in pregnant women. β agonist use is again a cornerstone of therapy, and in this regard, we usually recommend terbutaline. Terbutaline has been prescribed extensively and appears to be nonteratogenic, at least during the latter stage of pregnancy. Other β agonists have been used in Europe for long periods without complications. Occasionally, tachycardia, hypoglycemia, and tremor are seen in neonates exposed to these agents prenatally; however, these effects are treatable and reversible. Long-acting β agonist preparations have not been studied in pregnancy and are thus not recommended.

Cromolyn sodium, a nonsteroidal anti-inflammatory compound used to help attenuate the early and late-phase asthmatic responses following allergen exposure, has been used safely during pregnancy. The medication is available in a nasal or oral inhaled form, or as an ophthalmologic preparation. Its relative safety and benign side effect profile often justify a trial.

Theophylline has been used extensively during pregnancy, largely as an aid in controlling symptoms of nocturnal asthma. Clinical efficacy has been well documented. However, the narrow therapeutic window limits the medication to patients in whom close drug serum levels may be monitored. In pregnancy, maximum serum theophylline levels should not exceed 12 μg/mL. Newborns exposed to higher levels have experienced vomiting, tachycardia, and jitteriness. If theophylline is added to the regimen, we recommend it be reserved for cases in which inhaled corticosteroids and β-agonist had failed to provide adequate control. Doses should be titrated up to efficacious levels slowly, as opposed to loading the patient rapidly. This allows for more careful monitoring of symptoms of theophylline toxicity in the mother.

The use of inhaled, oral, and parenteral corticosteroids has been examined in human pregnancy extensively. No increased incidence of birth defects has been noted in the offspring of steroid-treated women. Although chronic systemic steroid use has been associated with a slight increase in premature deliveries and low-birthweight infants, these effects are minimal when weighed against the effects of maternal hypoxemia on the fetus because of uncontrolled asthma. Of the inhaled corticosteroid preparations available, beclomethasone has had the largest human experience during pregnancy and, thus, is used exclusively. Other preparations have not had sufficient study to warrant their use. As with all medications, careful consideration of the risk: benefit ratio is advised, and the lowest possible dose providing clinical efficacy should be empirically determined and utilized.

EXERCISE-INDUCED BRONCHOSPASM

The diagnosis and treatment of patients with EIB is becoming more common as the population increases efforts to stay fit. We have previously discussed the temporal effects of exercise on airway obstruction in susceptible individuals. It bears repeating that

exercise-induced symptoms may afflict up to 80% of patients with asthma. EIB is believed by some not to be a variant of asthma, but rather a characteristic response to a fairly common stimulus. It represents an early stage in the continuum of disease development. That is, many patients will manifest exercise-induced symptoms of airway obstruction as their initial presentation of asthma. Eventually, most will go on to develop other asthma-inducing stimuli, although there is a paucity of data addressing this phenomenon. This section will deal with patients who present with symptoms of asthma only when provoked by exercise.

EIB is a temporary increase in airway resistance that develops approx 10 or 15 min after completing strenuous exertion (Fig. 11). Interestingly, there is an initial increase in the baseline $FEV_{1.0}$ early during exercise, representing the normal physiologic response to exercise. In patients with EIB, this dilation is soon followed by bronchoconstriction, perhaps mediated by temperature fluxes in inspired air (as previously discussed). The bronchoconstriction lasts approx 1 h and is usually self-limited, often resolving spontaneously without treatment. The acute bronchospasm is followed by a 2-h refractory period, during which the airway is relatively immune to the effects of further exertion. Some asthmatics will proceed to develop a late-phase asthmatic response several hours later.

The diagnosis of EIB is made following a history suggestive of the condition. Wheezing, chest tightness, cough, or dyspnea during or shortly after exercise should arouse suspicion. The key to making the diagnosis is objective documentation of airflow obstruction following an exercise challenge, and subsequent reversibility after the exercise is completed. This can be done using PEFR measurements "in the field" or spirometry in the pulmonary function laboratory. Laboratory standards for exercise challenge testing have been established and are beyond the scope of this chapter. However, a decrease of 10% in either PEFR or $FEV_{1.0}$ after exercise is diagnostic of EIB.

There are several nonpharmacologic interventions that may prove useful in the treatment of EIB. The inhalation of warm, moist air during exertion is beneficial in preventing symptoms of EIB, as experienced while swimming. The addition of a mask or scarf will aid in warming inhaled air while running, skiing, or playing football or hockey. Such accouterments may not be apropos for competition, but may be useful for training. A more suitable measure for preventing EIB is a proper warm-up. It has been shown that proper warm-up exercises will result in the induction of a refractory period to EIB in up to 50% of patients. For example, an athlete may induce an asymptomatic refractory period by performing warm-up exercises 30–60 min prior to the onset of exercise. Multiple 30-s sprints performed at 2-min intervals prior to strenuous exercise may reduce the severity of EIB. This refractory period may last up to 2 h.

Most cases of EIB are amenable to pharmacological interventions. The cornerstone of EIB prophylaxis is use of a β agonist some 10–20 min prior to exercise. This should provide up to 4 h of protection during exercise. All agonists are efficacious. However, only albuterol and terbutaline are approved by the US and International Olympic Committees for use in competition. We treat several patients who engage in more strenuous, marathon events. These patients seem to benefit from the longer-acting β agonists, such as salmeterol. The drug must be administered 1–2 h prior to exertion and has met with great success in select patients. The addition of a cromolyn compound (either cromolyn

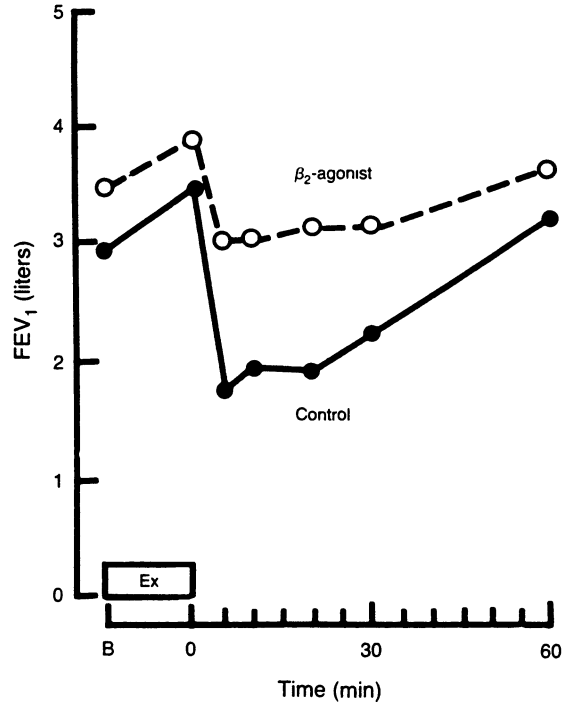

Fig. 11. Typical airway obstruction in a patient with EIB. This patient demonstrates characteristic airway dilation and rise in FEV_1 accompanying exercise (Ex), followed by a period of maximal bronchoconstriction 5 min after completion (solid line). This exercise-induced attack resolved spontaneously after 1 h. Some protection is noted by prophylactic treatment with a β agonist (dash line). From ref. *6*, with permission.

sodium or nedocromil) is recommended if the β agonist alone is insufficient. These compounds suppress both the early and late-phase reactions, and should be used immediately prior to exercise (within 5 min). These compounds are also approved for use in Olympic competition. Failure to control adequately symptoms of EIB with β agonists and cromolyn compounds usually necessitates referral to a specialist for definitive management.

EIB can easily be diagnosed and treated in the majority of patients. Individuals with asthma should be encouraged to enjoy a normal, active lifestyle, which includes a regular program of exercise. Asthma symptoms should not interfere with the desire to remain active and physically fit.

CONCLUSION

Asthma is one of the most common diseases seen in the primary care setting. An appreciation of the common triggers, underlying pathophysiology, and diagnostic approaches to the disease will enable the clinician to devise treatment regimens responsibly on an individual basis. Although most clinicians are confident and competent in the

management of the asthmatic patient, prompt recognition of unusual clinical presentations or incomplete responses to treatment will allow for referral to the specialist before asthma becomes uncontrollable.

The development of a close relationship with the asthmatic patient, and the recognition that he or she is an integral member of the team caring for the disease will lead to an improved outcome and higher quality of life.

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9 Rhinitis

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CONTENTS

INCIDENCE

Rhinitis clearly is one of the most frequent problems encountered in the outpatient practice of medicine. It is the most common IgE-mediated disease. In its allergic form, it affects approx 25 million Americans. The chronic nonallergic form afflicts at least five million more. The illness accounts for over 3.5 million lost workdays.

The mean age of onset of allergic rhinitis is between 8 and 11 yr. The prevalence of allergic rhinitis decreases with age. The mean age of onset of nonallergic rhinitis is much later in life. There is an equal incidence in males and females.

FUNCTIONS OF THE NOSE

The functions of the nose are noted in Table 1. Humidification, warming, and filtration are accomplished by the turbinates. The structure of the turbinates causes turbulent airflow. This enhances hydration, temperature control, and filtration. Air can be humidified to between 75 and 95% saturation and warmed from 25 to 37°C by the nose before it reaches the larynx. Particles 10 μ or more are completely filtered. Filtration efficiency will decrease as particle size lessens. The nose is not capable of filtering particles 2 μ or less.

Humidification and warming are accomplished in part via a sophisticated rheostat device that varies the size of the turbinates and affects the volume of nasal secretions. This is accomplished through the submucosal neurovascular network contained within the turbinates. Capillary flow empties into a capacitance system of sinusoids, which in turn empty into postcapillary venules. Sphincters control the capillary and postcapillary venule flow. In this way, fluid can accumulate in the sinusoids and thus vary the size of

From: *Allergic Diseases: Diagnosis and Treatment*
Edited by P. Lieberman and J. Anderson Humana Press Inc., Totowa, NJ

Table 1
Functions of the Nose

Conduit for airflow
Processing air
Humidification
Warming
Filtering
Defense
Antibacterial
Antiviral
Olfaction
Nasal reflexes
Voice resonance

the turbinates. The sinusoid reservoir will fill when the capillary sphincters are open and the postcapillary venule sphincters are closed. Emptying occurs when the distal sphincters are open and the proximal contracted. This system of sinusoid filling and emptying is controlled by the autonomic nervous system. Sympathetic stimulation will contract the proximal sphincters, thus emptying the reservoir. Parasympathetic stimulation can produce the opposite effect. However, the main effect of parasympathetic stimulation is to increase the volume of secretions.

The turbinates shrink and swell in a cyclical and reciprocal fashion. This cycle is owing to the alternating discharge of the sympathic nervous system. For example, when the inferior turbinate on the left is swollen, its counterpart on the right is contracted. At the same time, the middle turbinate on the left is contracted and its counterpart on the right swollen. Completion of the cyclical swelling and shrinking is accomplished in most people in about 60–90 min. As shrinking occurs, humidification is produced by a "sponge-like" squeezing of water vapor into the nasal airway during turbinate contraction.

Symptoms of nasal congestion are produced as the turbinates swell. Therefore, a knowledge of activities that affect turbinate size (Table 2) is important. Lying on one's back causes bilateral turbinate swelling, which is exaggerated in patients with rhinitis. Lying on one side produces swelling on the dependent side whereas the turbinates on the opposite side shrink. Chilling of the skin can produce turbinate congestion, as can inhalation of cold air. Hormonal changes of pregnancy and menses often produce turgescence of the turbinates. Aerobic exercise is a "natural nasal decongestant."

DIFFERENTIAL DIAGNOSIS AND PATHOGENESIS

The major tool in establishing the differential diagnosis of rhinitis is the history. The important elements of the history useful in establishing a differential diagnosis are noted in Table 3.

The physical examination is less helpful than the history in distinguishing between allergic and nonallergic rhinitis, but is essential to rule out mechanical or anatomical abnormalities. These include septal deviation, tumors, nasal polyps, synechiae connecting the turbinates and the septum, and septal perforation. Nasal exam is best accomplished

Table 2
Factors Affecting Turbinate Size

Factor	*Swelling*	*Shrinking*
Lying on back	+	
Lying on side	+ (Dependent side)	+ (Superior side)
Chilling skin	+	
Strong odors	+	
Warming skin		+
Pregnancy	+	
Menses	+	
Pain		+
Exercise		+
Breathing cold air	+	
Emotions:		
Frustration	+	
Fear		+
Anxiety	+	
Sexual stimulation	+	
Hyperventilation	+	

The most useful tool in the differential diagnosis of rhinitis is the history. Two most common forms of chronic rhinitis are allergic and chronic nonallergic. These can usually be distinguished by features of the history.

Features that suggest allergy are:

- Seasonal variation with exacerbations in spring and fall;
- Exacerbation on exposure to aeroallergens (e.g., animals and fresh cut grass);
- Association with other allergic conditions, especially conjunctivitis.

by anterior rhinoscopy using a strong light source and nasal speculum. Fiberoptic or rigid scope rhinoscopy is optimal to view the posterior nasopharynx, but is not indicated in every patient.

Allergy skin tests are the definitive tool for distinguishing allergic from nonallergic rhinitis. In vitro tests, because of their relative lack of sensitivity and expense, should be reserved for patients in whom skin testing is not possible for such reasons as a generalized dermatitis. Nasal smears are helpful in determining whether or not a patient will respond to topical corticosteroids. The presence of nasal eosinophilia usually indicates there will be a satisfactory response to topical corticosteroids. In addition, smears are useful in establishing the diagnosis of chronic nonallergic rhinitis with eosinophilia (NARES). Total IgE levels are not indicated because of the overlap existing between values in allergic and nonallergic individuals. Sinus roentgenograms and CT scans of the sinus are indicated when sinusitis is suspected. The differential diagnosis of rhinitis is seen in Table 4. The three most common forms are allergic, chronic nonallergic, and rhinitis owing to an upper respiratory tract infection.

Table 3
Features of the History Designed to Establish the Cause of Rhinitis

- Age of onset
- Chronological variations in symptoms
  - Perennial without seasonal variation
  - Perennial with seasonal variation
  - Seasonal
- If seasonal or with seasonal variation, denote specific months
- Exacerbating factors
  - Allergens:
    - Fresh cut grass, animal exposure, house dust, and hay
  - Irritants
    - Cigaret smoke, odors, perfumes, detergents, soap powder
    - Particulate dust
    - Automobile exhaust fumes
  - Nature of symptoms
    - Congestion
    - Sneezing
    - Pruritus
    - Postnasal drainage
    - Anterior rhinorrhea
    - Unilateral vs bilateral
  - Ingestants
    - Alcohol
    - Spicy foods
    - Other
  - Weather conditions
    - Weather fronts
    - Changes in humidity and temperature
    - Damp humid weather
    - Cold air
  - Environmental exposures
    - Workplace
    - Home
    - Pets
    - Feathers
    - Air conditioning, heating
  - Medications used to treat rhinitis and response to same
    - Topical
    - Oral
  - Medications used for other conditions
    - Topical
    - Oral
      - Antihypertensives
      - Birth control pills
      - Tranquilizers
  - Family history of atopy
  - Other personal manifestations of atopy
      - Asthma
      - Atopic dermatitis
      - Allergic conjunctivitis
  - Hobbies and activities

Table 4
Differential Diagnosis of Rhinitis

- Allergic
  - Seasonal
  - Perennial
- Chronic idiopathic nonallergic
  - NARES
  - Neurogenic (vasomotor)
- Upper respiratory infection
- Mechanical-anatomic obstruction
  - Tumors
  - Nasal polyps
  - Granulomas
    - Sarcoid
    - Wegener's
  - Septal deviation
  - Septal perforation
  - Foreign bodies
- Drug-induced (rhinitis medicamentosa)
  - Topical agents
    - α-Adrenergic vasoconstrictors
    - Cocaine
  - Oral agents
    - Antihypertensives
    - Birth control pills
    - Phenothiazines
  - Eye drops
- Endocrinologic
  - Pregnancy
  - Hypothyroidism
  - Acromegaly
- Acute cholinergic-induced rhinitis
  - Gustatory
  - "Skier's-jogger's nose"
- Cerebrospinal leakage
- Atrophic

ALLERGIC RHINITIS

Allergic rhinitis is produced by the degranulation of mast cells and basophils secondary to the union of IgE and allergen. The contents of these cells and their putative role in the production of symptoms of rhinitis are seen in Table 5. Histamine is probably the most important of these mediators in the production of immediate symptoms, but other mediators probably play a role in causing prolonged and recurrent symptoms.

The allergic reaction in the nose occurs in two phases. Symptoms begin 3–10 min after inhalation of allergen. Sneezing is the first to occur, followed shortly thereafter by an increase in secretions and then nasal congestion. Often symptoms abate, only to recur 2–4 h later. The first phase is called the early phase reaction, and the second phase, the late-phase reaction. The late phase is the result of the influx of cells into the nasal

Table 5
Relationship Between Symptoms and Mediators in Allergic Rhinitis

Symptom	*Pathophysiology*	*Mediator*
Obstruction	Increased vascular permeability and vasodilatation	Histamine, kinins, leukotrienes, neuropeptides
Rhinorrhea	Direct action on sensory nerve fibers	Histamine
	Reflex, cholinergic activity	Neuropeptides Leukotrienes
Sneeze	Stimulation of sensory nerve fibers	Histamine
Nasal hyperirritability	Infiltration of cells, especially eosinophils and basophils	Platelet activating factor Tumor necrosis factor Interleukins
Itching	Stimulation sensory nerves	Histamine
Loss of smell	Chronic inflammation	Summation effect of multiple mediators

mucosa. These cells are brought to the site by chemoattractants released from mast cells and basophils during the early phase. The most important of these cells are probably basophils and eosinophils. The late-phase reaction can produce a state of hyperirritability of the turbinates, making them more sensitive to aeroallergens as well as respiratory irritants. Clinical features characteristic of allergic rhinitis include exacerbations on exposure to allergens, such as fresh cut grass and animals, associated atopic manifestations, including allergic conjunctivitis, atopic dermatitis, and asthma, and often a seasonal variation, with symptoms increasing in the spring and fall (Table 6).

Chronic Nonallergic Rhinitis

The pathogenesis of chronic nonallergic rhinitis is unknown. Chronic nonallergic rhinitis is not a specific disorder, but refers to chronic rhinitis for which no other diagnosis can be made. Therefore, it is a diagnosis of exclusion.

Chronic nonallergic rhinitis probably has many different causes. For example, about 15–20% of patients with this syndrome have an increase in eosinophils in their nasal secretions. The acronym NARES has been used to refer to this condition. Other patients have secretions with abundant neutrophils and no eosinophils. As opposed to allergic rhinitis, which usually begins in childhood or adolescence, the age of onset of chronic nonallergic rhinitis is most commonly in the middle years.

Most patients with chronic nonallergic rhinitis have perennial symptoms, but there is often a seasonal exacerbation. They are made worse by exposure to respiratory irritants, such as cigarette smoke and perfumes, rather than by exposure to allergens, such as fresh cut grass and animal danders. Weather conditions usually play a prominent role in the production of symptoms. These include weather fronts, changes in temperature and humidity, and damp weather. Posterior nasal drainage is usually more common than in the allergic form. Table 6 summarizes the clinical features that differentiate allergic and nonallergic rhinitis.

Table 6
The Differential Diagnosis Between Allergic and Nonallergic Rhinitis

Manifestation	*Allergic rhinitis*	*Chronic nonallergic rhinitis*
Age of onset	Usually before 20	Usually after 30
Seasonality	Usually with seasonal variation, spring and fall	Usually perennial, but frequently worse during weather changes, such as those occurring during fall and early spring
Exacerbating factors	Allergen exposure	Irritant exposure and weather conditions
Nature of symptoms		
Pruritus	Common	Rare
Congestion	Common	Common
Sneeze	Prominent	Usually not prominent, but can be dominant in some cases
Postnasal drainage	Not prominent	Prominent
Other related manifestations, e.g., allergic conjunctivitis, atopic dermatitis	Often present	Absent
Family history	Usually present	Usually absent
Physical appearance	Variable, classically described as pale, boggy swollen—may appear normal	Variable, erythematous
Ancillary studies	Allergy skin tests always positive	Allergy skin tests negative
Nasal eosinophilia	Usually present	Present 15–20% of the time (NARES)
Peripheral eosinophilia	Often present, especially during allergy season	Absent

Upper Respiratory Tract Infections

Upper respiratory tract infections can be confused with acute exacerbations of allergic or nonallergic rhinitis. This is especially true when infections occur during the pollen season in patients with the allergic form of the disease. Usually, however, after the first 72 h, the diagnosis becomes evident. Features that point toward an upper respiratory tract infection are the presence of fever, sore throat, lymphadenopathy, unilateral purulent conjunctivitis, and purulent drainage.

Mechanical and Anatomical Obstruction

There should always be a high index of suspicion for mechanical and anatomical obstruction in patients with rhinitis. Tumors and foreign bodies are usually unilateral. Tumors are commonly associated with a unilateral maxillary and/or ethmoid sinusitis. Foreign bodies may also be associated with maxillary sinusitis. In both there may be unilateral nasal bleeding and a unilateral purulent nasal discharge.

Nasal polyps are usually bilateral. They can usually be distinguished from turbinates by their color. They are most often a pearl gray color and have a smooth mucoid appearance. In addition, in contrast to normal turbinates, they are mobile and nonpainful to manipulation. Polyps can be missed on anterior rhinoscopy and are best seen by utilizing a rhinoscope.

Patients with septal perforation often complain of nasal obstruction even though such obstruction is not seen on examination. The sensation of obstruction results from an aberration in nasal airflow.

Drug-Induced Rhinitis (Rhinitis Medicamentosa)

By far the most common cause of rhinitis medicamentosa is over-the-counter α-adrenergic vasoconstrictors. These drugs produce an initial decongestion followed by a "rebound" effect, whereby the size of the turbinates actually increase after the effect of the vasoconstrictor subsides. The rebound usually does not occur until the drug has been used for several days. Because of this rebound effect the patient is induced to use the vasoconstrictor once more. After prolonged use, the duration of effect is reduced, and the frequency of use therefore increases. This can result in the use of such vasoconstrictors on almost an hourly basis. Inhaled cocaine can cause a similar problem. In addition, oral medications, especially certain antihypertensives (α-adrenergic blocking agents) can produce rhinitis. As with topical vasoconstrictors, the symptoms are dominated by nasal congestion. Birth control pills, in susceptible individuals, can produce similar symptoms. Of note is the fact that the chronic use of eye drops can also produce rhinitis. This is because of absorption of the agents through the nasolacrimal duct. Both medication and preservatives in eyedrops can cause congestion as well as rhinorrhea.

Endocrinologic Rhinitis

Pregnancy is the most common form of endocrinologic rhinitis. The turbinate vessels have estrogen receptors that, in susceptible patients, mediate turgescence with swelling of the turbinates. Hypothyroidism and acromegaly can also result in chronic nasal congestion. The turbinates are especially sensitive to growth hormone.

Acute Cholinergic-Induced Rhinitis

Gustatory rhinitis and "skier's-jogger's nose" are both the result of cholinergic activity. Cholinergic discharge occurs with eating in the former and with exposure to cold air in the latter. The most prominent symptom is a profuse rhinorrhea. The rhinorrhea is clear and copious. It begins shortly after eating or exposure to cold air. The incidence of gustatory rhinitis increases with age.

Cerebrospinal Fluid Leakage

Rhinitis owing to leakage of cerebrospinal fluid is characterized by a clear, watery, unilateral or bilateral rhinorrhea. The rhinorrhea becomes more profuse when the head is tilted forward and the patient "bears down." The flow is usually sufficient to allow collection of several milliliters in a beaker over a period of 30 mins. Cerebrospinal fluid can be distinguished from normal nasal secretions because it contains glucose. A "dipstick" analysis will suffice to detect the presence of glucose in the secretions.

Atrophic Rhinitis

Atrophic rhinitis is a relatively rare condition. It is the result of withering of the turbinates and a decrease in volume of nasal secretions. It usually occurs in the elderly, but rarely can occur in younger patients. The symptoms are bilateral and consist of a thick discharge with very little congestion. There is often postnasal drainage. Secondary bacterial growth occurs, and the patient complains of an odor. It is perennial, but usually worse in the winter.

THERAPY

The mainstay of therapy for rhinitis is pharmacologic management. When the patient has allergic rhinitis, environmental control and allergen immunotherapy may also be indicated. Pharmacologic management is achieved through the use of H_1 antihistamines, decongestants, anticholinergics, cromolyn sodium, and corticosteroids.

Antihistamines

First-Generation Antihistamines

H_1 antagonists are competitive inhibitors of histamine. They bind to the H_1 receptor and are traditionally classified as first- and second-generation drugs. First-generation drugs pass the blood–brain barrier and therefore can produce drowsiness. Second-generation drugs do not pass the blood–brain barrier at all or do so poorly. They therefore do not produce drowsiness at normal therapeutic doses.

First-generation drugs have been divided further on the basis of structure into six groups, ethanolamines, alkylamines, ethylenediamines, piperazines, piperidines, and phenothiazines. Each group is said to have individual characteristics that bestow certain therapeutic qualities (Table 7). At the time of this writing, there are four nonsedating antihistamines available in the United States. These are terfenadine, astemizole, loratadine, and cetirizine.

Antihistamines have other pharmacologic actions that can enhance therapeutic activity or produce side effects. The most prominent of these is limited to first-generation antihistamines. These drugs can have significant anticholinergic activity. This is useful in the control of symptoms resulting from cholinergic discharge (rhinorrhea and sneezing), but can also produce side effects (difficulty urinating, dry mouth, blurred vision). Other antihistamines have anti serotonergic effects, and can inhibit the release of histamine from basophils and mast cells.

All antihistamines are rapidly absorbed from the gastrointestinal tract. All presently available antihistamines are metabolized in the liver via the cytochrome P_{450} system, except for cetirizine, which is secreted through the kidney and therefore does not depend on hepatic metabolism. Hepatic dysfunction or drugs that interfere with cytochrome P_{450} activity can affect the metabolism of these drugs.

Antihistamines have tissue lives extending beyond measurable serum levels. Thus, their therapeutic effect is present long after the drug is metabolized. However, the onset of tissue effect is delayed relative to peak serum levels. This is perhaps one reason why efficacy is improved when these drugs are used prior to exposure to allergen. The pharmacokinetic and pharmacodynamic characteristics of selected H_1 antagonists are seen in Table 8.

Drugs Useful in the Therapy of Rhinitis

- Antihistamines—especially good for sneezing and rhinorrhea.
- Decongestants—useful only for nasal stuffiness and congestion.
- Anticholinergic agents—useful for anterior rhinorrhea.
- Mast cell stabilizers—especially useful for pretreatment prior to aeroallergen exposure, such as before mowing the lawn.
- Corticosteroids—the most potent of all agents and useful for all symptoms.

Antihistamines are particularly effective for sneezing, rhinorrhea, and pruritus. They have less effect on postnasal drainage and are relatively ineffective for control of nasal congestion. Thus, they are usually more helpful in acute, seasonal allergic rhinitis than in chronic, perennial allergic rhinitis in which congestion may be more pronounced. They are probably more beneficial in allergic than in chronic nonallergic rhinitis. There is no clear-cut evidence to indicate that a patient becomes tolerant to a given preparation, nor is there any evidence to indicate that one drug is particularly of more benefit than another.

The most common side effect of first-generation antihistamines is drowsiness. About a third of patients experience this complaint. Of note is the fact that patients can exhibit delayed reaction time, inability to concentrate, and other cognitive dysfunctions without the subjective sensation of drowsiness. This means that such patients may be at risk if operating machinery or driving, even though they are unaware of any impairment. Drowsiness can be overcome with effort, but more subtle impairment of cognitive function persists until the effect of the drug abates.

The antimuscarinic activity of first-generation antihistamines accounts for the second most frequent group of side effects. These include dysuria with urinary retention, blurring of vision, dry mouth, and constipation.

Second-Generation Antihistamines

Second-generation, nonsedating antihistamines do not cause drowsiness nor do they produce anticholinergic side effects. Terfenadine and astemizole have been associated with arrhythmias, most notably torsades de pointes. Episodes of arrhythmias have usually been the result of overdoses, decreased catabolism because of hepatic dysfunction, or the simultaneous administration of another drug metabolized via the cytochrome P_{450} system. Under these circumstances, both terfenadine and astemizole prolong the QT interval by interfering with the delayed potassium rectifier channel, thus delaying repolarization. Therefore, these drugs should not be administered with ketoconazole, itraconazole, or erythromycin. In addition, it is reasonable to assume that caution is advisable in regard to their simultaneous administration with other drugs that are metabolized through the cytochrome P_{450} system or in patients with liver disease, hypocalcemia, hypokalemia, and congenital prolongation of the QT interval. Fexofenadine (released in the United States in 1996), the active metabolite of terfenadine, does not effect cardiac conditions.

The four second-generation antihistamines are not equivalent drugs in terms of their pharmacokinetics and pharmacodynamics. The onset of action of astemizole is somewhat delayed, and the drug has an extremely long half-life. Thus, there is a question re-

Table 7
Characteristics of Representative First-Generation H_1 Antagonists Based on Chemical Classification

Chemical class	*Examples*	*Comments*
Ethanolamines	Diphenhydramine Clemastine Carbinoxamine	Significant antimuscarinic effects; can be potent sedatives, but sedative potential varies, with clemastine producing the least amount; can have some antimotion sickness activity
Alkylamines	Chlorpheniramine Brompheniramine Tripolidine Dexchlorpheniramine Acrivastine	Relatively moderate incidence of drowsiness; moderate anticholinergic effect; no antiemetic or antimotion sickness activity; few gastrointestinal side effects
Ethylenediamines	Tripelennamine Antazoline Pyrilamine	Mild to moderate sedation; slight anticholinergic effect; some local anesthetic effect; as a group said to have frequent gastrointestinal side effects
Piperazines	Hydroxyzine Cyclizine Meclizine	Meclizine and cyclizine have relatively low sedative activity with main use being for vertigo, antimotion sickness, and antiemetic activity; hydroxyzine has significant anticholinergic activity; it is useful in therapy of chronic urticaria
Piperadines	Azatadine Cyproheptadine Phenindamine	Mild to moderate sedation; little anticholinergic activity, antiemetic activity, and antimotion sickness activity; cyproheptadine has potent antiserotonin effect and can cause increased appetite
Phenothiazines	Promethazine Trimeprazine Methdilazine	Usually highly sedating; mainly used as antiemetics

garding whether this drug is appropriate on an "as-needed" basis or for use in women of childbearing age (since it persists in tissues for several weeks after cessation of therapy). Astemizole, loratadine, and cetirizine can be administered on a once daily basis. Terfenadine and fexofenadine are commonly prescribed at a dose of 60 mg b.i.d., but in some instances, 120 mg taken daily exert a similar effect. Both terfenadine and loratadine are available with a decongestant (pseudoephedrine). Astemizole and cetirizine are not available with a decongestant: A comparison of these five drugs is seen in Table 9.

Decongestants

Decongestants act by stimulating the α-adrenergic receptor controlling the capillary sphincters at entrance to the venous plexuses of the turbinates. They act only on turbinate swelling and have no effect on other manifestations of rhinitis. Topical appli-

Table 8
Pharmacodynamic Characteristics of Selected First-Generation H_1 Antagonists[a]

Drug	*Approximate time at which peak serum concentration is reached after oral dose, h*	*Approximate half-life, h*	*Approximate duration of biological activity, suppression wheal and flare*
Chlorpheniramine	1.5–2.5	20–24	24
Diphenhydramine	0.75–2.5	8–9	6–10
Brompheniramine	2–3	24	9
Hydroxyzine	1 to 2.5	20	36
Tripolidine	1–2	2.1	—

[a]The route of metabolism for all listed drugs is the liver.

cation is more effective and rapid in onset than oral administration; however, as noted, topical use beyond a few days can cause rhinitis medicamentosa. Therefore, the use of topical decongestants should be limited to 1 wk. They do, however, have a role in the therapy of sinusitis, upper respiratory tract infections, and the prevention of barotrauma and otitis occurring during air travel. Table 10 lists the decongestants available for use. There is no clear-cut drug of choice in this group. When a topical decongestant is used, a long-acting drug is probably preferable if for no other reason than convenience.

Oral decongestants can cause side effects, including nervousness, insomnia, and difficulty urinating, especially in patients with prostate enlargement. Other side effects are infrequent. Although there is a well-known admonition not to prescribe these drugs to patients with hypertension, they appear to be safe in patients with mild to moderate, stable hypertension. Topical decongestants have few side effects other than for the induction of rhinitis medicamentosa and the predisposition, with prolonged use, toward septal perforation. However, if these drugs are used in large doses, they can cause the same side effects seen with oral decongestants.

Anticholinergics

Anticholinergics are beneficial primarily for therapy of patients with anterior, clear watery rhinorrhea. Therefore, they are excellent for the treatment of gustatory rhinitis and "skier's-jogger's nose." They also can alleviate the anterior rhinorrhea associated with upper respiratory tract infections.

A major advance in anticholinergic therapy of rhinitis occurred with the introduction of aqueous ipratropium bromide (Atrovent). Ipratropium bromide, unlike naturally occurring anticholinergic agents (Belladonna alkaloids), does not pass the blood–brain barrier and therefore can be administered relatively free of side effects. It is available in two concentrations (0.03% and 0.06%). The 0.03% preparation is extremely useful in the treatment of perennial rhinitis in both its allergic and nonallergic forms. It is especially effective in patients with prominent rhinorrhea. The 0.06% preparation is useful for a 2-wk therapy of rhinorrhea caused by the common cold. In addition, it is useful in the therapy of gustatory rhinitis (skier's/jogger's nose). The dose of both preparations is 1–2 squirts each nostril b.i.d. to t.i.d. or 1 h before eating, exposure to cold, and so forth. Side effects are rare. The most common is probably nasal dryness and irritation.

Anticholinergic agents are also available in oral forms administered in conjunction

Table 9
Pharmacokinetic and Pharmacodynamic Characteristics of Terfenadine, Astemizole, Loratadine, Fexofenadine, and Cetirizine

	Approximate time at which peak serum concentration is achieved, h	*Approximate half-life, h*	*Biological activity, suppression of histamine-induced wheal and flare*			*Dose, mg*	*Available with decongestant*	*Route of metabolism*
			Approximate time of onset, h	*Approximate peak activity, h*	*Approximate duration of significant activity, h*			
Terfenadine and fexofenadine	1/2–1	Plasma half-life 4–5 h with terminal elimation half-life of active metabolites 16–24 h	1–2	3–4	8–12	60 b.i.d. dose 1 b.i.d.	Pseudoephedrine	Liver (Terfenadine) Kidney (Fexofenadine)
Astemizole	1	24 h for parent compound and 168–264 for active metabolite	Significant inhibition of wheal and flare does not occur after single dose but only appears after multiple dosing (usually d 2)	Maximum inhibition usually occurs between d 9 and 12 of multiple daily doses	After multiple daily dosing, skin test suppression can persist for weeks	10 q.d.	No	Liver
Loratadine	1		1–3	8–12	>24	10 q.d.	Pseudoephedrine dose 1 b.i.d.	Liver
Cetirizine	1	Mean half-life 8 h; terminal elimination half-life 20 h	1–2	4–8	24	10 q.d.	No	Primarily kidney

Table 10
Decongestants

Oral
Pseudoephedrine
Phenylpropanolamine
Phenylephrine
Topical long-acting (8–12 h)
Oxymetazoline
Xylometazoline
Topical short-acting (3–8 h)
Tetrahydrozoline
Naphazoline
Phenylephrine

with antihistamine-decongestant preparations. Oral agents can cause blurred vision, difficulty urinating, dry mouth, and nasal irritation owing to decreased secretions. Combination drugs containing antihistamines-decongestants with anticholinergic agents are noted in Table 11.

Cromolyn Sodium

Cromolyn sodium inhibits both the early and late-phase allergic reactions. Although its mechanism of action is not completely understood, it does prevent mast cell degranulation. It is effective in allergic rhinitis, but not in nonallergic rhinitis. It is especially effective in the seasonal form of allergic rhinitis. It is also very useful in preventing symptoms owing to isolated allergen exposure, for example, prior to mowing the lawn or visiting someone with a pet.

Cromolyn sodium is administered before exposure. When treating seasonal allergic rhinitis, it is best started a week prior to the allergy season. During the season, it must be used on a regular basis. It usually requires administration three to four times a day. Cromolyn sodium is almost devoid of side effects.

Corticosteroids

Corticosteroids are the most effective drug for therapy of rhinitis in both its allergic and nonallergic forms. Oral therapy is more effective and rapid in onset than topical therapy. A week to 10-d course of prednisone (or equivalent) beginning at 40–50 mg/d and tapering to discontinuation is almost universally effective in controlling symptoms of rhinitis regardless of cause. This regimen is recommended prior to the initiation of topical therapy with either cromolyn sodium or corticosteroids when the nasal mucosa is inflamed. Pretreatment in this way reduces the exacerbation of symptoms that can occur with the initiation of topical treatment as applied to an inflamed nasal mucosa. Six drugs are presently available for topical use. These are beclomethasone, triamcinolone, flunisolide, dexamethasone, budesonide, and fluticasone (Table 12).

Topical dexamethasone is probably the most potent of these agents. However, because this drug is absorbed in its active form, it is more likely to produce detectable, although modest, systemic effects. This limits its usage. Nonetheless, the drug is clearly appropriate for treatment of seasonal rhinitis lasting no longer than 6 wk. The

Table 11
Selected Combination Antihistamine, Decongestant, and Anticholinergic Agents

Trade name	*Antihistamine*	*Decongestant*	*Anticholinergic*
Seldane-D[a]	Terfenadine	Pseudoephedrine	—
Claritin-D[a]	Loratadine	Pseudoephedrine	—
Trinalin	Azatadine maleate	Pseudoephedrine	—
Semprex-D	Acrivastine	Pseudoephedrine	—
Polyhistine-D	Phenyltoxolamine citrate	Phenylpropanolamine HCl	—
Duravent DA	Chlorpheniramine maleate	Phenylephrine HCl	Methscopolamine nitrate
Extendryl SR	Chlorpheniramine maleate	Phenylephrine HCl	Methscopolamine nitrate

[a]Contains nonsedating, second-generation antihistamine.

other topical agents have high topical:systemic ratios of activity and are catabolized more rapidly. Therefore, they exert little if any systemic effect in recommended doses. In addition, topical side effects, even after prolonged use, are minimal. Nasal irritation is probably the most common side effect. Nasal bleeding, especially when blowing the nose, occurs with significant frequency, especially during the winter months. Unprovoked nasal bleeding can also occur and should prompt discontinuation of the drug. Nasal septal perforation has been reported, and patients should be monitored for this side effect. Because of the possibility of the occurrence of a septal perforation, care should be taken to avoid directing the spray at the septum. The patient should be instructed to point it away from the midline and toward the ear of the side they are spraying.

There is no clear-cut drug of choice among the agents with high topical; systemic ratios of activity. Three of these agents, triamcinolone, budesonide, and fluticasone, can be used once a day. They are, therefore, convenient to use. Another criterion for selection may be the delivery system. Beclomethasone and fluticasone are available as aqueous agents. Some patients prefer the aqueous delivery system, and others the metered dose aerosol.

A clear-cut limit on the duration of use of topical corticosteroids (other than dexamethasone) has not been established. It is clear (with the exception of dexamethasone) that they can be used for at least several months. Nasal biopsy specimens and cultures obtained from patients using topical corticosteroids continuously for several years have shown no significant mucosal atrophy, or fungal or bacterial overgrowth. However, patients taking these drugs long-term should be monitored, especially for the occurrence of bleeding on the septum, which may be a harbinger of a perforation.

THERAPY OF SPECIFIC FORMS OF RHINITIS

Seasonal Allergic Rhinitis

Mild seasonal allergic rhinitis can be controlled with antihistamines alone, or with a combination of an antihistamine and decongestant. If sedation occurs, a nonsedating antihistamine can be employed during the day. If symptoms do not respond to these

Table 12
Topical Corticosteroid Preparations Used to Treat Rhinitis

Drug	*Trade name*	*Type of delivery*	*Dose*		*Sprays/container*
			Adults	*Children*	
Beclomethasone	Beconase	Fluorocarbon aerosol	1 spray = 42 μg 1–2 sprays each nostril b.i.d. to t.i.d.	6–12 yr: 1 spray each nostril t.i.d. 6–12 yr: 1–2 sprays each nostril b.i.d.	200
	Beconase AQ	Liquid spray		6–12 yr: 1 spray each nostril t.i.d.	
	Vancenase	Fluorocarbon aerosol		6–12 yr: 1–2 sprays each nostril b.i.d. (No beclomethasone preparation approved for use in children under 6 yr)	
	Vancenase AQ	Liquid spray			
Triamcinolone	Nasacort	Fluorocarbon aerosol	1 spray = 55 μg 2 sprays each nostril q.d. to b.i.d.	Not approved for children under 12 yr	100
Flunisolide	Nasalide	Liquid spray	1 spray = 25 μg 1–2 sprays each nostril b.i.d.	6–14 yr: 1 spray each nostril t.i.d. Not approved for children under 6 yr	200
Dexamathasone	Turbinaire Dexacort	Fluorocarbon aerosol	1 spray = 0.1 mg 1–2 sprays each nostril b.i.d. to t.i.d.	6–12 yr: 1–2 sprays each nostril b.i.d. Not approved for children under 6 yr	170
Budesonide	Rhinocort	Fluorocarbon aerosol	1 spray = 32 μg 2 sprays each nostril b.i.d. or 4 sprays q.d.	6–12 yr: 2 sprays each nostril b.i.d. or 4 sprays q.d. Not approved for children under 6 yr	200
Fluticasone	Flonase	Liquid spray	1 spray = 50 μg 1–2 sprays each nostril q.d.	6–12 yr: 1 spray each nostril b.i.d. Not approved for children under 6 yr	60 or 120

agents, topical corticosteroids or cromolyn sodium can be added. In a child, cromolyn sodium may be the drug of choice, but the necessity to administer it several times a day can be limiting. Dexamethasone can be used without worry of significant side effect for seasonal allergic rhinitis not extending beyond 8 wk.

Perennial allergic rhinitis in both its allergic and nonallergic forms usually requires long-term therapy with topical corticosteroids. Dexamethasone should not be used in this setting, but beclomethasone, flunisolide, triamcinolone, budesonide, and fluticasone are safely administered for several months. Antihistamine-decongestants can be used as supplements. Ipratropium 0.03% is also useful for perennial allergic and nonallergic rhinitis, especially in patients with prominent rhinorrhea. Some patients require intermittent short courses (7–10 d) of oral corticosteroids.

As noted, cholinergic rhinitis (gustatory and "skier's-jogger's nose") can usually be controlled with preventive application of ipratropium bromide 0.06% used before eating or exercise in cold air.

Rhinitis medicamentosa is treated with a 7–10 d course of prednisone and a topical corticosteroid (usually dexamethasone). On the third day of prednisone administration (once the inflammation of the mucosa has been diminished), a topical corticosteroid is added to the prednisone therapy. The topical corticosteroid should be continued 4–6 wk. The patient should be instructed to discontinue the topical decongestant within the first week of initiation of therapy. However, to avoid discomfort, this does not have to be done precipitously. The patient can taper off the topical decongestant gradually over a period of 1 wk. Oral decongestants can be used as needed.

Nasal polyps can be shrunk with corticosteroids. The treatment is similar to that of rhinitis medicamentosa, except that often larger doses of prednisone given over a slightly longer period of time (10 days to 3 wk) and the chronic use of topical steroids are indicated. The initial dose of prednisone should be 50–60 mg a day in an adult, which can be tapered to a dose of 10 mg over 2 to 3 wk. At the same time, a topical corticosteroid should be started. In such cases, topical corticosteroid therapy may be needed indefinitely. Recurrence is common. During recurrences, the patient is again treated with oral corticosteroids. Often a polypectomy can be avoided using this regimen. However, if patients require more than three courses of prednisone per year or do not obtain adequate relief, a polypectomy may be indicated.

Rhinitis of pregnancy is particularly difficult to control because of the admonition against using drugs, especially during the first trimester. The only effective drug in most instances is corticosteroids or topical nasal decongestants. The latter should be avoided because of the risk of rhinitis medicamentosa. The decision to initiate either oral or topical corticosteroid therapy should be made in conjunction with the obstetrician. In most instances, during the last trimester, topical corticosteroids are fairly effective and can be given without any significant side effect. Dexamethasone should be avoided in this instance. Rhinitis of pregnancy usually worsens as the pregnancy proceeds, but abates spontaneously on parturition.

Nonpharmacologic Measures

For patients with allergic rhinitis, environmental control can be extremely helpful and, in some instances, curative. For example, if the patient has rhinitis resulting from

Table 13
Complications of Rhinitis

Disturbances of facial growth and development
Increased length of face
Retrognathic maxilla and mandible
Crossbite
High arched palate
Otitis media
Sinusitis
Disturbance of taste and smell
Nasal polyps
Sleep interruption and sleep apnea
Activation of nasal-bronchial reflexes

allergen, the removal of the pet may be all that is needed to eliminate the problem. Patients allergic to grass pollen should avoid mowing the lawn, and patients allergic to dust mite should institute an antidust mite environmental control regimen. These measures are discussed in detail in Chapter 22.

Allergen immunotherapy is an effective measure in allergic rhinitis. It is indicated in patients intolerant of medication or inadequately controlled by medication, or who wish to try to eliminate symptoms and be free of the need for medication. Immunotherapy is discussed in detail in Chapter 23.

COMPLICATIONS

Complications of rhinitis are seen in Table 13. These include abnormalities in facial development and growth, otitis media, nasal polyps, sinusitis, activation of nasal reflexes, disturbances of olfaction and taste, and sleep disturbance.

Facial abnormalities are a particularly poignant problem in children with severe allergic rhinitis. Chronic mouth breathing produces disturbances in the growth of the maxilla and mandible, causing increased facial length, crossbite, retrognathic maxilla and mandible, and high arched palate. These can be cosmetically disturbing when the patient reaches full growth. These complications are one of the reasons to treat severe allergic rhinitis aggressively in childhood. Sinusitis and otitis media result from obstruction of the sinus ostia and the eustachian tube, respectively.

Disturbances of olfaction and taste can be extremely bothersome to patients. They are particularly difficult problems to control in patients with severe rhinitis. Often congestion, drainage, and other symptoms respond to topical corticosteroids, leaving only altered smell and taste.

It is not clear whether nasal polyps are actually a complication of rhinitis or rather a coexisting problem. The polyps themselves can predispose to sinusitis, and sinusitis is present in almost all instances of nasal polyposis. There is significant evidence that nasal obstruction predisposes to bronchoconstriction through the activation of nasal reflexes. Thus, control of rhinitis is considered helpful in the treatment of asthma. Sleep disturbances, including sleep apnea, can occur as a result of rhinitis. Treatment of the rhinitis is often helpful in reducing the severity of sleep apnea.

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10 Sinusitis and Otitis Media

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CONTENTS

SINUSITIS

Definitions and Epidemiology

Sinusitis is a clinical condition characterized by mucosal inflammation of the paranasal sinuses. Acute sinusitis is a rapid-onset bacterial infection that has been present for <1 mo and most commonly affects the maxillary sinuses. Subacute sinusitis, with symptoms present between 1 and 3 mo, usually develops when an acute episode of bacterial sinusitis has not been adequately treated. Chronic sinusitis has been present for at least 3 mo and is often associated with persistent mucosal changes.

Sinus disease is frequently encountered in general practice, and it has been estimated that 0.5% of viral upper respiratory infections result in acute sinusitis. Chronic sinusitis is also a very common condition and afflicts at least 31 million people in the United States.

Pathogenesis

Four host factors determine the susceptibility to sinusitis; patency of the ostia, ciliary function, quality of secretions, and local host immunity. Obstruction of the sinus ostium leads to reduced oxygen content and the development of mucosal edema and serum transudation within the sinus cavity. These alterations foster bacterial growth, reduce ciliary movement, and alter leukocyte function. If an acute episode of sinusitis occurs, the sinus will usually return to normal following effective antibiotic treatment. However, if therapy is incomplete or underlying etiologic factors are not treated, persistent changes may occur in sinus anatomy and physiology. Factors that have been associated with sinusitis are listed in Table 1.

From: *Allergic Diseases: Diagnosis and Treatment*
Edited by P. Lieberman and J. Anderson Humana Press Inc., Totowa, NJ

Table 1
Conditions Associated with Sinusitis

Obstruction of the sinus ostia
Acute viral rhinitis
Chronic rhinitis (allergic and nonallergic)
Nasal polyps
Adenoidal inflammation and enlargement
Septal deviation
Aerated middle turbinate
Foreign body (nasogastric tube)
Dental infection
Physical phenomena
Barotrauma (flying, diving, swimming)
Air pollution
Systemic diseases
Antibody-deficiency syndrome
Down's syndrome
Cystic fibrosis
Wegener's granulomatosis
Ciliary dyskinesia syndrome

Clinical Presentation

Acute Sinusitis

The most consistent feature distinguishing acute bacterial sinusitis from a viral respiratory infection is persistence of symptoms beyond 7–10 d. Cough and nasal discharge are the two most common complaints in children, whereas headache and facial pain are unusual in children younger than age 10. Adult patients with acute sinusitis most often complain of discolored nasal discharge, unilateral facial pain, headache, and cough. Although only reported in a minority of patients, upper tooth pain is a very specific diagnostic finding in sinusitis.

On examination, high temperature and signs of toxicity are unusual and should prompt a search for complications, such as meningitis or periorbital abscess. Anterior rhinoscopy frequently reveals erythematous, swollen turbinates and purulent secretions on the floor of the nose. However, the absence of pus does not rule out active infection, since sinus drainage may be intermittent. Facial tenderness elicited by palpation is an unreliable sign in differentiating sinusitis from acute rhinitis. Transillumination may be useful in evaluating acute maxillary and frontal sinusitis in adults if interpretation is confined to extremes of light transmission (i.e., clear vs opacified sinus cavity).

Chronic Sinusitis

Patients with chronic sinusitis usually present with indolent symptoms of nasal congestion, thick postnasal drip, and cough. Adult patients may also complain of facial fullness and headache. Secondary eustachian tube obstruction or middle ear fluid may result in popping of the ears and muffled hearing. In addition to these chronic complaints, patients may also experience recurrent exacerbations of symptoms resembling acute sinusitis.

Symptoms Suggestive of Sinusitis

- Acute disease
  - Persistence of URI symptoms, usually without fever, beyond 7–10 d
  - Children: cough, nasal discharge; adults: discolored nasal discharge, unilateral facial pain, headache, cough
- Chronic disease: long-standing nasal congestion, thick postnasal drip, cough, facial fullness, sore throat, and hearing problems

Physical examination often demonstrates swelling and erythema of the inferior and middle turbinates and occasionally mucopurulent secretions on the floor of the nose and middle meatus. Nasal polyps may be present and usually originate from the middle meatus. In children, middle ear effusions are present in half of all cases and serve as excellent clues to the presence of sinusitis. Transillumination is not useful in evaluating chronic sinus disease, since mucosal thickening usually yields equivocal results. Flexible fiberoptic rhinoscopy is a useful and easily learned procedure that can help identify important anatomic lesions not visible by anterior rhinoscopy, including posterior deviation of the nasal septum, nasal polyps, enlargement or inflammation of the adenoid, or tumor.

Diagnostic Tests

In many patients with acute and chronic sinusitis, diagnosis and subsequent therapy can be based on the history and physical findings. However, in a significant number of patients, signs and symptoms may be equivocal, and additional testing is required to make a diagnosis.

Laboratory Tests

Cytologic examination of freshly stained nasal secretions (using Hansel's or modified Wright-Geimsa media) is a convenient and inexpensive technique for evaluating nasal complaints. Significant neutrophilia (>5 neutrophils/high-power field) is a sensitive but nonspecific predictor of sinusitis, whereas nasal eosinophilia is highly predictive of allergic rhinitis and normal sinus X-rays. Nasal cytology is most helpful in excluding the possibility of sinusitis when eosinophils are present and/or neutrophils are absent. The peripheral white blood count/differential and nasal swab cultures have no utility in determining the presence of infection or in accurately identifying pathogenic bacteria in sinusitis.

Imaging Studies

Although plain radiography has recently fallen out of favor in evaluating sinusitis, we feel that this technique continues to play a helpful role in selected patients. Although plain X-rays accurately visualize the maxillary and frontal sinuses (particularly the Water's occipitomental view), the ethmoid and sphenoid sinuses are difficult to assess. Water's view findings that are diagnostic of sinusitis include a sinus air–fluid level, sinus opacification, or severe mucosal thickening (>50% of antral diameter in children and >8 mm in adults). In patients with possible acute sinusitis who have failed initial medical therapy, a plain film is useful in documenting infection before prescribing addi-

Confirmation of Chronic Sinus Disease

- CT of the sinuses is believed to be "the Gold Standard," but is relatively expensive, and requires sedation in children younger than 8 yr.
- Plain radiographs
  - Air–fluid levels
  - Opacifications
  - Mucosal thickening (children: more than 50% of antral diameter; adults: >8 mm)
- Nasal cytology, transillumination only of some help; magnetic resonance imaging (MRI) most important in detecting soft tissue abnormalities

tional, more expensive antibiotics. When evaluating possible chronic sinusitis in children, a Water's view is also helpful, since the maxillary sinuses are usually the principal sinuses involved. In adults with chronic sinusitis, however, plain films may yield false-negative results, since infection is limited to the ethmoid sinuses in up to 40% of cases.

Computed tomography (CT) provides a detailed view of the ethmoid and sphenoid sinuses, and the ostiomeatal complex regions. Recently, a "screening" sinus CT (4–10 cuts) has become widely available. In conjunction with an otolaryngologist, a CT should be performed in patients who have persistent or recurrent symptoms suggestive of sinusitis despite adequate medical therapy. CT scanning should be delayed if a viral upper respiratory infection has recently occurred, since 85% of patients have transient abnormalities on CT following a cold. CT imaging of the sinuses should always be used judiciously, since even the "screening" scan remains a relatively expensive test and does require sedation for most children younger than 8 yr of age.

MRI is extremely sensitive in detecting subtle soft-tissue abnormalities of the paranasal sinuses. For this reason, it is the technique of choice in imaging suspected sinus neoplasms, fungal infections, and complicated infections that extend intracranially. MRI should not be used for routine diagnosis of sinusitis since it is very costly and does not adequately visualize the bony landmarks required for surgical planning. Sinus ultrasound is rarely used as a diagnostic test owing to its poor sensitivity and specificity in patients with both acute and chronic sinusitis.

Maxillary Aspiration and Culture

Referral should be made to an otolaryngologist for maxillary aspiration when acute sinusitis is associated with signs of severe toxicity (particularly in hospitalized or immunosuppressed patients) or is unresponsive to an adequate trial of appropriate antibiotics.

Microbiology

Acute Sinusitis

The most commonly identified organisms in children with acute sinusitis are *Streptococcus pneumoniae* in 30–40%, *Haemophilus influenzae* in 20–25%, and *Moraxella catarrhalis* in 20%. In adults, *S. pnuemoniae* and *H. influenzae* are the two leading causes of sinusitis, whereas *Moraxella* is unusual. Anaerobic organisms are primarily

identified in cases of acute sinusitis originating from dental root infections, but are otherwise uncommon. Hospital-acquired sinusitis is most often seen as a complication of nastogastric tube placement and is typically caused by gram-negative enteric organisms, such as pseudomonas and klebsiella species.

Chronic Sinusitis

Bacterial isolates in children with chronic sinusitis are usually the same as those seen in acute disease. In children with more severe and protracted symptoms, anaerobic species (such as bacteroides) and staphylococci are cultured more frequently. Anaerobic organisms predominate in adults with chronic sinusitis, with species of bacteroides and anaerobic cocci accounting for nearly 90% of the isolates.

Fungal organisms, such as aspergillus species, are a common cause of sinus disease in immunocompromised hosts, including diabetics and patients with defective cell-mediated immunity. Increasingly, fungi have been identified as causes of sinusitis in patients who are otherwise healthy and should therefore be considered in cases of refractory sinusitis. Allergic fungal sinusitis is a syndrome that occurs in adults with asthma and has been attributed to aspergillus, bipolaris, and curvularia species. It is characterized by severe, hyperplastic sinusitis and nasal polyposis, and is associated with significant eosinophilia of sinus tissue and blood.

Medical Therapy

Acute Sinusitis

Antibiotics are the primary form of treatment for acute sinusitis. Amoxicillin, taken for 10 d, remains the initial drug of choice, except in regions where there are very high rates of β-lactamase producing strains of *H. influenzae*. In cases of penicillin allergy, trimethoprim-sulfamethoxazole is a suitable alternative, but erythromycin is inadequate for most infections. Symptoms begin to improve with these antibiotics within 3 d in 75% of cases. If patients show no improvement with the initial antibiotic after 3–5 d, they should be given an alternative, β-lactamase-resistant agent for 10 additional days. Amoxicillin-clavulenate, cefuroxime, cefprozil, cefpodoxime, loracarbef, and clarithromycin have all proven to be effective in treating acute sinusitis. In patients who have improved incompletely after 10 d of therapy, the same antibiotic should be given for 7–10 additional days. Symptoms recurring soon after a course of antibiotics are usually owing to the original organism and should be treated with an alternative β-lactamase-resistant agent for 21 more days. In patients who do not respond to empiric therapy, sinus aspiration and culture may be indicated to guide additional treatment.

Topical and oral decongestants reduce nasal congestion associated with acute sinusitis and may reduce ostial edema, allowing for improved sinus drainage. Mucolytic agents, such as guaifenesin, are occasionally helpful in patients who complain of abundant, thick secretions. Older antihistamines with strong anticholinergic effects, such as diphenhydramine and hydroxyzine, may cause mucus inspissation and impede sinus drainage. However, the newer, nonsedating antihistamines, such as loratadine and terfenadine, have virtually no anticholinergic effects and can be continued in patients who require these agents for concomitant allergic rhinitis.

Chronic Sinusitis

Although there are few published data regarding antimicrobial therapy for chronic sinusitis, anecdotal evidence suggests that patients should be treated for a minimum of 21 d. In patients who have not been previously treated with antibiotics, amoxicillin is a cost-effective choice for first-line therapy. In patients who are allergic to penicillin, clarythromycin provides good coverage against most relevant pathogens. If the patient has not responded to these drugs within 10 d, an alternative β-lactamase-resistant antibiotic should be given for 21 additional days. For adult patients who do not improve with this treatment, agents with increased anaerobic coverage, such as clindamycin or metronidazole, may be effective.

In addition to antibiotics, topical nasal corticosteroids should be prescribed for 3–6 wk to reduce mucosal edema and inflammation. If severe turbinate swelling or nasal polyps are present, a 5–7 d course of prednisone (0.5 mg/kg/d given in 2–3 divided doses) is often very effective. Both topical and oral corticosteroids appear to be safe in chronic sinusitis, and there is no evidence that they increase the risk of intracranial extension or fulminant infection when given to patients with normal immune function. In allergic patients and patients with nasal polyposis, chronic use of nasal corticosteroids may be helpful in preventing recurrences of sinusitis.

Nasal irrigations, performed two to three times daily with a bulb syringe and saline, can be very helpful in removing dried secretions. Other methods to increase nasal humidification (hot showers, room humidifiers, and steam inhalers) are easy to use and may provide symptomatic relief for short periods of time.

Surgical Therapy

Patients with chronic sinusitis refractory to medical therapy should be referred to an otolaryngologist for consideration of surgery. In children with persistent maxillary sinus disease, antral lavage (with or without adenoidectomy) effectively removes purulent material and often provides long-lasting symptom relief. In adults, however, functional endoscopic surgery has largely supplanted other surgical procedures and is effective in 50–80% of patients. Patients with aspirin-sensitive asthma, nasal polyposis, and pansinusitis are more likely to have recurrent disease and should be discouraged from undergoing multiple repeat surgeries.

Patients suspected of having intracranial complications (e.g., periorbital abscess, brain abscess, or meningitis) of acute sinusitis should be referred for immediate surgical consultation. Cardinal signs and symptoms include high fever, severe headache, proptosis, and changes in mental status.

Evaluation of Patients with Recurrent or Persistent Sinusitis

Fifty percent of children and 30–40% of adults with recurrent or chronic sinusitis are sensitized to common aeroallergens, such as plant pollens, house dust mite, and animal danders. Allergy skin testing should be performed in these patients, since they often benefit from a comprehensive program of allergen avoidance, antiallergic drug therapy, and in selected cases, immunotherapy. Patients with severe, recurrent episodes of sinusitis associated with other infections (e.g., otitis, bronchitis, and pneumonia) may suffer from one of the antibody-deficiency syndromes and should undergo a screening assessment of their immunoglobulin levels. If a deficiency is noted or still suspected after

the initial testing, these patients should be referred to an allergist/immunologist for further evaluation.

OTITIS MEDIA

Definitions and Epidemiology

Acute otitis media (AOM) refers to an acute suppurative infection of the middle ear space that usually lasts for 3 wk or less. Otitis media with effusion (OME; previously referred to as "secretory" or "serous" otitis media) represents persistent middle ear fluid that most often follows an episode of AOM and may last for many months. Recurrent AOM is defined as three or more episodes of AOM during the preceding 6 mo.

AOM is the most frequently diagnosed disease of children and is unusual in adult patients. It occurs in roughly 60% of children by age one and in 80% by age three. Half of all children have had three or more episodes of AOM by age three. Otitis media with effusion is similarly common, noted in approximate 50% of patients during the first year of life.

Pathogenesis

The two factors that contribute most significantly to otitis media are eustachian tube dysfunction and bacterial proliferation in the nasopharynx. The functions of the eustachian tube include pressure equalization, protection of the middle ear from nasopharyngeal secretions, and mucociliary clearance of the middle ear. Eustachian tube obstruction results in the development of negative pressure, which is followed by serum transudation into the middle ear. This sterile effusion may become infected by bacteria refluxing from the nasopharynx into the middle ear. Incomplete eradication of an initial infection or prolonged underventilation of the middle ear may ultimately result in a chronic, mucoid effusion. Table 2 lists conditions commonly associated with otitis media.

Clinical Presentation

AOM

Children with AOM typically complain of acute unilateral ear pain, which occurs several days after a viral upper respiratory infection. The symptoms frequently start early in the morning and are associated with irritability and fever, although nausea, vomiting, and diarrhea are not common. Otoscopy usually reveals a red, thickened, and bulging tympanic membrane. Insufflation (pneumatic otoscopy) generally demonstrates poor mobility of the drum. Importantly, the drum may also appear red in a crying child (owing to increased vascularity of the tympanic membrane) and may lead to an incorrect diagnosis of AOM.

OME

Children with this chronic condition are usually asymptomatic, but may have a subtle loss of hearing. There is usually no recent history of fever, irritability, or other systemic symptoms. The eardrum may appear yellow, orange, or blue, and is often retracted. Air-fluid levels or bubbles may be present, and the drum moves poorly with insufflation. Unfortunately, if middle ear fluid is very thin, mobility may appear normal even to

Table 2
Risk Factors for Development of Otitis Media

Anatomic causes of eustachian tube dysfunction
Viral upper respiratory infection
Allergic rhinitis
Chronic sinusitis
Tonsillar hypertrophy (including adenoids)
Cleft palate disease
Variants of eustachian tube anatomy
Systemic diseases
Down's syndrome
Ciliary dyskinesia syndrome
Immunodeficiency
Epidemiologic factors
Male gender
Absence of breast feeding
Race: Native Americans >> Whites >> Blacks
Overcrowding
Air pollution
Cigarette smoking (mother)

highly trained observers. Physical findings suggestive of allergic rhinitis, sinusitis, or tonsillar hypertrophy should be sought, since these conditions may play important pathogenic roles in OME.

Diagnostic Tests

Electroacoustic Impedance (Tympanometry)

Tympanometry is a convenient, simple procedure that is extremely sensitive in detecting middle ear fluid. Otitis media can be confidently ruled out when tympanometry is normal.

Audiometry

In children older than 18 mo, audiometry is an important test in determining whether OME has resulted in hearing loss. This test should be employed when middle ear fluid has been present for at least 3 mo before deciding whether ventilation of the middle ear is necessary.

Diagnostic Tympanoscentesis

Tympanoscentesis with culture of middle ear fluid is indicated in children who are are extremely ill with AOM, children who have not responded to an adequate trial of appropriate medical therapy, and children in intensive care nurseries.

Microbiology

The three principal organisms identified in middle ear effusions from both AOM and OME are the same as those isolated from patients with acute sinusitis. *S. pneumoniae*, nontypable *H. influenzae*, and *M. catarrhalis* are isolated in 35, 23, and 14% of effu-

Otitis Media with Effusion (OME)

- A chronic condition, usually in otherwise asymptomatic children
- Subtle hearing loss
- Often follows AOM and may last for several months
- More common with associated allergic rhinitis, chronic sinusitis, and tonsillar hypertrophy

sions, respectively. Other organisms that are occasionally cultured include *Staphylococcus aureus*, alpha streptococcus, and group A streptococcus. Special exceptions include very young infants and children in intensive care nurseries, in whom group B streptococci and gram-negative organisms are very common causes of AOM.

Medical Therapy

AOM

Although placebo-controlled studies have demonstrated that many children will recover from AOM without treatment, antibiotics do reduce the duration and severity of signs and symptoms. More importantly, antibiotics have reduced the incidence of and death rate from suppurative complications of AOM. For initial episodes, amoxicillin is the drug of choice and should be given for 10–14 d. Trimethoprim-sulfamethoxazole is a good alternative in penicillin-allergic patients. In most cases, symptoms should improve significantly within 2–3 d. If symptoms persist, a second-line antibiotic with β-lactamase resistance (see Acute Sinusitis) should be given for an additional 10–14 ds.

Adjunctive measures, including antihistamine-decongestant combinations and topical nasal corticosteroids, have not been proven to be effective in children with AOM. However, these agents may have a beneficial effect with concomitant allergic rhinitis.

Recurrent AOM

Prophylactic antibiotics have been shown to be effective in reducing the number of episodes of AOM in children who are prone to recurrence. Amoxicillin (20 mg/kg/d) and sulfisoxazole (50 mg/kg/d) are used most commonly, and treatment should be continued through the high-risk URI seasons (late fall to early spring). Pneumococcal vaccine should also be encouraged in all children over age 2 who suffer from recurrent otitis.

OME

Although at least 80% of effusions resolve spontaneously within 2 mo, effusions that persist for longer than 3 mo will not usually improve without therapy. The most effective medical therapy for OME is probably a 14-d trial of amoxicillin. More potent antimicrobial agents or longer courses of antibiotics have not been shown to be helpful. Adjunctive measures (antihistamine-decongestants, topical corticosteroids) have also not been shown to be effective. Antibiotic therapy for OME should be considered in children with associated sinusitis, or those who have a documented conductive hearing loss, vertigo, or tinnitus, structural changes in the tympanic membrane or middle ear, or in infants who are unable to describe symptoms. Following antibiotic therapy, the effusion must be followed carefully to ensure resolution.

Surgical Therapy

If medical therapy for recurrent AOM or OME is ineffective or poorly tolerated, a patient should be referred for evaluation by an otolaryngologist. Myringotomy with tube placement is effective in reducing the frequency of acute infections and in decreasing the duration of chronic effusions and their associated hearing loss. If tube placements are not effective, or a child has persistent adenoidal infection or enlargement, adenoidectomy with repeat tube placements has been shown to be beneficial in children older than age 4. Tonsillectomy has not been shown to provide any additional benefit over adenoidectomy alone.

Evaluation of Patients with Recurrent AOM or OME

Thirty to 40% of children with recurrent AOM and OME have associated nasal allergy. These patients should undergo allergy testing and, if indicated, a complete program of allergen avoidance and antiallergic drug therapy prior to surgical intervention. Children with very severe, recurrent episodes of AOM associated with intracranial complications or bronchial infections should undergo an evaluation of their humoral immunity.

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11 Diagnosis and Treatment of Allergic Diseases of the Eye

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CONTENTS

ROUTES OF EXPOSURE TO ALLERGENS, IRRITANTS, AND DRUGS

Allergens and other ocular irritants can be deposited directly onto the surface of the eye from the surrounding environment, deposited on hair and skin, or rubbed, wiped, or washed into the eye. There is a net flow with gravity of sebum and trapped particles from the hair that can easily enter the eye. Substances can also gain access to ocular tissue via the systemic circulation. Many agents can be concentrated and secreted in tears, causing allergic or irritative conjunctivitis. Finally, compounds have a more difficult route of entry into the posterior structures of the eye. The cornea and the lens serve as an effective barrier for most agents that are administered topically, and there is a blood–retinal barrier, analogous to the blood–brain barrier, that protects the eye from the systemic circulation. Molecules cross this barrier based on size, charge, and lipid solubility.

Inflammation of surrounding skin, mucosa, or even sinuses can more or less spill over into the eye. Inflammatory products released nearby travel to ocular tissues and propagate inflammation.

ALLERGIC DISEASES OF THE EYE

Of all the possible ocular manifestations of allergic disease, allergic conjunctivitis is probably the most common. Conjunctivitis, in its entirety, is a broad term that describes

From: *Allergic Diseases: Diagnosis and Treatment*
Edited by P. Lieberman and J. Anderson Humana Press Inc., Totowa, NJ

Table 1
Differential Diagnosis for Conjunctivitis

Allergic origin
Allergic conjunctivitis
Blepharoconjunctivitis
GPC
Chemical- or drug-induced conjunctivitis (inclusive of contact dermatitis)
Vernal conjunctivitis
Nonallergic origin
Bacterial conjunctivitis (most likely organisms?)
Viral conjunctivitis (adenovirus, EPK)
Chlamydial conjunctivitis
Foreign body
Acne rosacea
Keratoconjunctivitis sicca
Chemical- or drug-induced conjunctivitis
Carotid and dural sinus fistulae
Anterior uveitis
Episcleritis/scleritis
Factitious
Idiopathic

conjunctival inflammation. There are many causes of conjunctivitis, some of which are listed in Table 1. Appropriate treatment modalities for the various forms of allergic conjunctivitis are listed in Table 2. Most cases of conjunctivitis are easily treated when properly diagnosed and resolve without loss of vision. A good history of symptoms, medications, previous allergies, and underlying pathology, as well as a good slit lamp exam is important for making the correct diagnosis.

Ocular allergies can manifest as conjunctivitis, blepharitis, eczema, and contact dermatitis. Because the eye has thin layers of tissue, it is prone to developing secondary infections, further complicating the clinical picture.

Acute Allergic Conjunctivitis

Acute or seasonal allergic conjunctivitis comprises approximately half of all cases of allergic conjunctivitis. It is a type I allergic reaction and commonly occurs with allergic rhinitis. The symptoms of allergic conjunctivitis can vary from time to time in the same patient and are often accompanied by other signs of allergic diseases.

The diagnosis of allergic conjunctivitis can usually be made on the basis of clinical findings and history. Common factors in patients with allergic conjunctivitis include an atopic personal or family history, seasonal variation in symptoms, and associations with exposure. At times the patient may be able to define the specific offending agent. Ocular signs of allergic conjunctivitis are listed in Table 3. The hallmark symptom that often distinguishes allergic conjunctivitis from other forms of conjunctivitis is pruritus.

Of use in differentiating allergic from other forms of conjunctivitis is a conjunctival scraping. After the administration of a topical local anesthetic, such as proparacaine, the palpebral conjunctiva (under the upper lid) can be gently scraped several times with a

Table 2
Treatment Options for the Various Forms of Allergic Conjunctivitis

Form	*Treatment*	*Duration*
Seasonal allergic conjunctivitis	Avoidance, antihistamines, topical mast cell stabilizers, Vasoconstrictors, Topical NSAIDS, corticosteroids	Seasonal or chronic
Vernal	Cold compresses, mast cell stabilizers, antihistamines, corticosteroids, analgesics	Abates by adulthood
Blepharoconjunctivis	Lid scrubs topical or systemic antibiotic or topical antibiotic/steroid combination	May be chronic
Contact conjunctivitis	Avoidance	
GPC	Abstain from contact lens wear, topical mast cell stabilizers, and topical antihistamines, change lens polymer or lens cleaning regimen	

Key Features of the Diagnosis of IgE-Mediated Allergic Eye Disease

There are three key features of IgE-mediated allergic eye disease:

- Pruritus, which is usually intense;
- Bilateral involvement, and
- Associated with atopic respiratory tract disease.

The absence of any of these is strong evidence against allergy as a cause of the condition.

spatula to obtain a tissue sample. The sample is spread on a slide and stained with May-Grunwald Giemsa or another appropriate stain to identify inflammatory cells, such as eiosinophils or neutrophils. The absence of inflammatory cells, however, does not rule out the diagnosis of allergic conjunctivitis. The presence of eosinophils strongly suggests allergic etiology.

Acute allergic conjunctivitis is most often bilateral, is rarely blinding, and has seasonal variations. Some patients suffer from allergic conjunctivitis throughout the year, most likely as a result of exposure to house dust and animal dander. Therapeutic options include avoidance, symptomatic relief with pharmacological agents, and immunotherapy. Avoidance should be the first line of treatment and should be included as a part of all therapeutic regimens. Pharmacologic therapy is divided into two categories, palliation and prophylaxis.

Vernal Keratoconjunctivitis

Vernal conjunctivitis is a chronic, bilateral catarrhal inflammation of the conjunctiva that is most commonly found in children and adolescents. Males tend to be affected more often than females, and it usually resolves by early adulthood. The effects of ver-

Table 3
Clinical Findings in Various Forms of Allergic Conjunctivitis

Type	*Clinical findings*
Seasonal allergic conjunctivitis	Itchy eyes with watery discharge, erythematous conjunctiva, eyelid edema, photophobia, foreign body sensation; often associated with rhinitis, but rarely with angioedema, asthma, and urticaria
GPC	Associated with soft contact lens wear, itchy eyes, decreased contact lens tolerance, blurred vision, giant papillae on upper tarsal conjunctiva
Vernal keratoconjunctivitis	Extreme itching, ropy mucous discharge, giant papillae on upper tarsal conjunctiva, Trantas' dots, corneal abrasions uncommon; may be associated with significant pain
Contact dermatoconjunctivitis	Thickening, scaling, fissures on eyelids, conjunctival injection, and chemosis
AKC	Itching, increased tearing, burning sensation, eyelids, papillary hypertrophy on lower and upper tarsal conjunctiva, corneal vascularization, ulcerations, and scarring
Microallergic conjunctivitis	Itching, increased tearing, ocular irritation, conjunctival and/or corneal phlyctenules

nal conjunctivitis can be so severe that blindness may result. Like allergic conjunctivitis, vernal conjunctivitis is thought to be immune-mediated. As with allergic conjunctivitis, patients have elevated tear levels of IgE and histamine. Conjunctival biopsies reveal increased numbers of eosinophils, basophils, mast cells, and plasma cells.

Vernal conjunctivitis usually occurs during the spring and summer months, but in severe cases may be perennial. The most remarkable finding of vernal conjunctivitis is intense itching and giant papillae on the tarsal conjunctiva (Fig. 1). Ropy mucoid discharges are also a distinguishing sign. In mild cases or early in the disease, the papillae may be absent, making a distinction between vernal and allergic conjunctivitis difficult. The cornea may also be involved with keratitis, epithelial erosions, and ulceration occurring in the more severe cases. Trantas' dots may be present at the superior limbus. In general, the tear concentrations of histamine and IgE are much higher in vernal conjunctivitis than in allergic conjunctivitis. In addition, IgG, C3, factor B, and C3 anaphylatoxin levels are elevated, indicating that additional factors play a role in the pathogenesis of vernal conjunctivitis. Vernal conjunctivitis probably represents a severe and chronic form of allergic conjunctivitis with more intense symptoms and sequelae.

Treatment of vernal conjunctivitis includes the aggressive use of topical mast cell stabilizers, topical antihistamines, and topical nonsteroidal anti-inflammatory agents. Corticosteroids should be used only in severe cases of vernal conjunctivitis, and then only until symptoms abate. Their use should be under the supervision of a primary eye care provider. Cold compresses often give good symptomatic relief and may be used as adjunct therapy. In severe cases, corneal epithelial defects can occur, causing the patient a great deal of pain and discomfort. Pain associated with this condition should be treated with appropriate analgesics and will usually resolve once the symptoms improve.

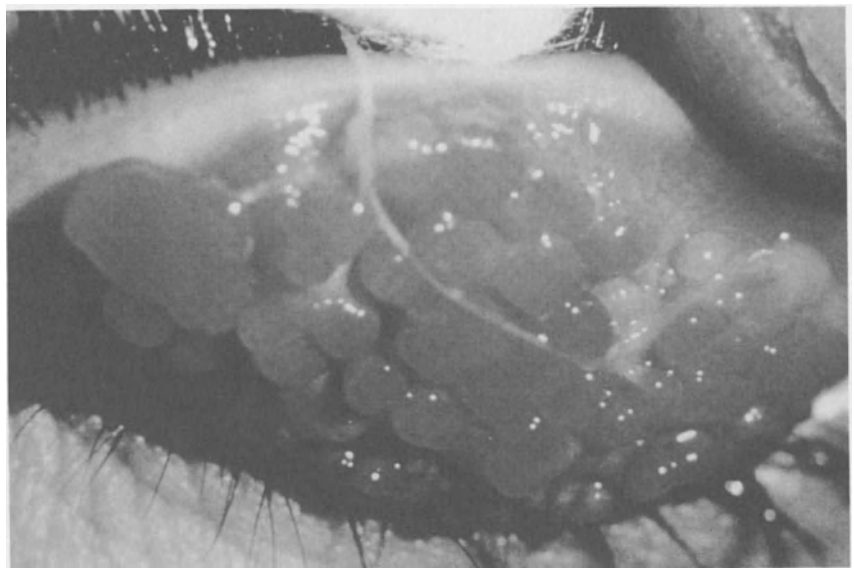

Fig. 1. Giant papillae on the tarsal conjunctival of a patient with vernal conjunctivitis. Photograph courtesy of Barbara Jennings.

Atopic Keratoconjunctivitis (AKC)

Atopic dermatitis, although usually manifesting peripherally, can have significant ocular findings. It has been estimated that up to 25% of patients with atopic dermatitis will often have ocular involvement, such as AKC. Ocular findings in AKC include conjunctivitis, keratoconjunctivitis, keratoconus, cataracts, and an increased risk for ocular infections. Other common ocular symptoms of AKC include intense pruritus, edematous, coarse, and thickened eyelids, conjunctivitis that resembles allergic conjunctivitis, and keratoconjunctivitis that is indistinguishable from vernal conjunctivitis. The itching and burning of the eye are often associated with photophobia and increased lacrimation. Corneal involvement from AKC includes superficial punctate keratitis, vascularization, ulceration, and scarring. The pathophysiology of AKC is not well known, but is thought to be related to a type I and type IV hypersensitivity reaction.

Keratoconus and cataract formation, although less frequent findings in patients with AKC, occur more frequently than in nonatopic patients. The etiologies of both are unknown. There does not appear to be an HLA haplotype that controls for keratoconus. The mechanism of cataract development is also not known. Because they are anterior cataracts as opposed to posterior, they are not related to corticosteroid use.

Treatment of AKC includes the use of corticosteroids for short periods of time, antihistamines, mast cell stabilizers, and cold compresses. Careful following of patients with AKC is necessary to prevent damage to vision.

Atopic Eczema of the Eyelids and Skin

Chronic dermatitis owing to allergy can affect the anterior ocular structures. The antigens can be from various sources, including particles trapped by the hair that moves down the face with sebum and irritates the periocular area. These include environmental

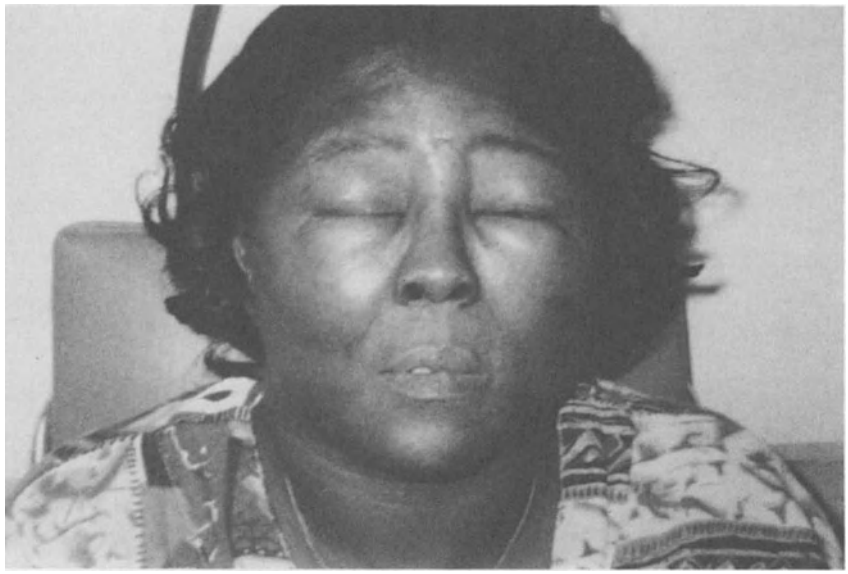

Fig. 2. Angioedema around the eyes 24 h after exposure to hair dye. Patient had a similar reaction to hair dye 2 mo previously.

irritants, drugs, inflammatory mediators, and cutaneous infections. Conjunctivitis associated with atopic eczema is characterized by conjunctival injection, gritty sensation, and ocular irritation. Breaks in the skin barriers from allergic disease and/or chronic use of topical corticosteroids make the patient with allergic disease prone to secondary cutaneous infections in and around the eye. It is important to be aware that even topical corticosteroids can promote cataract formation with chronic use and that they also predispose the patient to secondary ocular herpetic infections.

Contact Dermatoconjunctivitis

Contact allergies of the eye and periocular area occur with a variety of cosmetics, soaps, contact lens solutions, and medications. Symptoms include conjunctival injection, hyperemia, and edema of the lids and periocular area (Fig. 2). A careful history may assist in revealing a temporal relationship between the onset of symptoms and exposure, but in a significant percentage of contact-type reactions, the causative agent is not identified.

There are some compounds that have a high rate of producing contact reactions. These are listed in Table 4. Treatment of contact allergies includes removal and avoidance of the offending agent, cool compresses, ocular lubricants, antihistamines, and topical steroids. Secondary infections should also be adequately treated. Antigens associated with *Staph sp.* blepharitis can cause ocular irritation.

Giant Papillary Conjunctivitis

Giant papillary conjunctivitis (GPC) is increasingly more common with the advent of extended wear soft contact lenses. GPC is also associated with ocular sutures or the

Table 4
Agents with a High Incidence of Contact Allergic Reactions

Neomycin	Bacitracin
Thimerosol	Idoxyuridine
Atropine	Polymxin B
Papain	Benzalkonium chloride

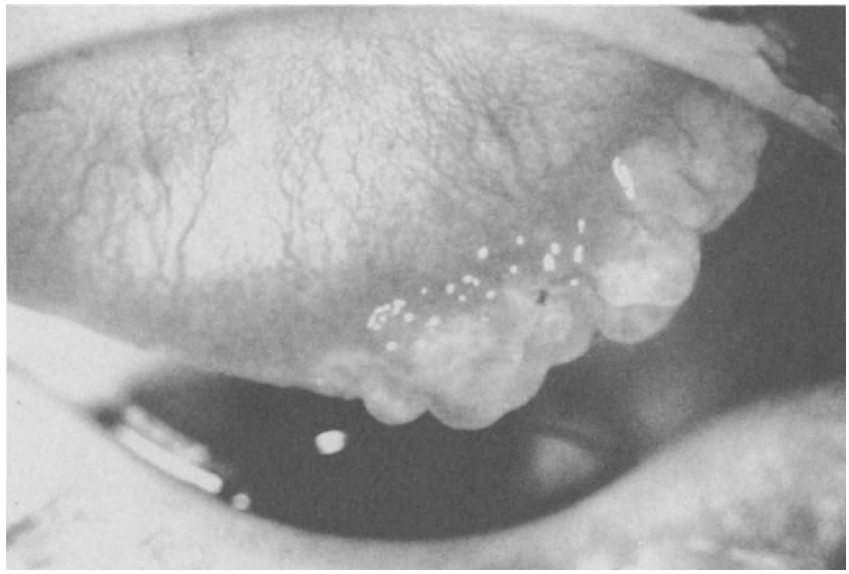

Fig. 3. GPC in a contact lens patient. Notice the giant papillae on inversion of the upper eye lid. Photograph courtesy of Tom Landgraf.

presence of other foreign bodies. It is thought that the antigen responsible for the inflammatory response is located on the surface of the foreign body. Contact lens wearers secrete a protein that coats the lenses, and it is believed that this protein coating is responsible for the allergic response. Histologic findings in GPC are similar to those of other allergic eye diseases. There is the presence of IgE, IgG, and IGM in the tears, and the presence of inflammatory cells in the conjunctiva, suggesting an immune-mediated mechanism.

Clinically, GPC is characterized by the presence of large papillae in the tarsal conjunctiva of the upper lid (Fig. 3). Patients often complain of intense itching, decreased tolerance to contact lens wear, blurred vision, conjunctival injection, and increased mucous production. GPC resembles vernal conjunctivitis, but is almost exclusively associated with contact lens wearers. GPC has also been reported in patients with ocular prosthesis, after cataract and corneal transplant surgery where sutures are in place.

Treatment involves corticosteroids, antihistamines, mast cell stabilizers, frequent enzymatic cleaning of the lenses, or changing the lens polymers. It will usually resolve when the patient stops wearing contact lenses or the foreign body is removed.

Table 5
Differential Diagnosis for Allergic Diseases of the Eye

	Seasonal	*Itching*	*FBS*	*Lid involvement*	*Bilateral*	*Discharge*	*Tearing*
Acute allergic conjunctivitis	Yes	Yes	No	No	Yes	Mucoid	Yes
Vernal keratoconjunctivitis	Yes	Yes	No	No	Yes	Stringy and tenacious, ropy	Yes
GPC	No	Yes	Yes	No	Yes	Mucoid	Yes
Dermatoconjunctivitis	No	Yes	No	Variable	Yes	Variable	Yes
Belpharoconjunctivitis	No	No	No	Yes	Yes	Morning matting	No change
Seborrheic dermatitis	No	No	No	Yes	Yes	None	No change
Bacterial conjunctivitis	No	No	Yes	Matting	Variable	Mucopurulent	Yes
Viral conjunctivitis	No	No	+/–	No	Yes	Watery	Yes

NONALLERGIC DIFFERENTIAL DIAGNOSIS

The differential diagnosis for ocular allergy includes several nonallergic conditions that can sometimes be clinically indistinguishable from true allergy (Table 5). Many irritants act directly on ocular tissues to produce inflammation through non-IgE mediated mechanisms. Many drugs can cause non-IgE-mediated degranulation of mast cells. Usually ocular allergy does not exist alone, but is associated with rhinitis, dermatitis, or asthma.

Allergic reactions, nonallergic direct irritation, and infection of the eye all result in inflammation. Clinically, inflammation from different causes is often indistinguishable. History and physical signs may help differentiate the causes of inflammation so the most appropriate treatment can be implemented. Once the barriers to the eye are broken down by chronic inflammation, secondary infection is common. On the other hand, with chronic infection, ocular tissues can become hypersensitive to a variety of substances, even the antigens produced by the infectious agent.

One of the distinguishing features of allergic disease is that it most commonly affects both eyes simultaneously. Conjunctivitis that is of bacterial or viral origin usually begins unilaterally, but may involve both eyes over time. Also, ocular allergic disease is associated with itching, viral and bacterial conjunctivitis are usually not, and tend to be almost asymptomatic or occasionally painful.

Blepharoconjunctivitis (Marginal Conjunctivitis)

Blepharoconjunctivitis is characterized by a chronic inflammation and erythema of the eyelid margin. Often it is owing to the presence of *Staphylococcal* bacteria. Rarely, blepharoconjunctivitis can be caused by other organisms, such as *Pasteurella multocida* and *Phthirus pubis*. Patients with blepharoconjunctivitis will often complain of awakening with their eyes matted shut and a crusty discharge along the eyelids. Pruritus is almost always absent. Basically, blepharitis is a problem of lid hygiene. Examination will show a yellow crusting of the eyelids with collarette formation at the base of the cilia and disorganized or missing cilia. If the exudates are removed, ulceration of the lid margin is often evident. Fluorescein staining of the ocular surface reveals punctate lesions on the inferior portion of the cornea. These punctate lesions are thought to be a result of bacterial exotoxin produced by the *Staphlococcus* organism.

Acute bacterial conjunctivitis from *Staphlococcus* is characterized by ocular irritation, conjunctival redness, and a mucopurulent discharge that is worse in the morning. The condition can be chronic, and treatment consists of lid margin scrubs, warm compresses and 7–14 d of anti-Staphlococcal antibiotics.

Viral Conjunctivitis

Viral conjunctivitis usually begins as a unilateral conjunctivitis of very abrupt onset and clears within 5–7 d. It may be associated with pharyngitis and a low grade fever, and can easily transmit from one eye to the other and from patient to patient. One of the hallmark differences between allergic conjunctivitis and viral conjunctivitis is the lack of pruritus with viral etiology. The most common organism in viral conjunctivitis is the adenovirus. The second eye may become involved a few days after the manifestations of the initial symptoms. Common findings of viral conjunctivitis include a watery dis-

charge, conjunctival injection, chemosis, and enlargement of the preauricular lymph nodes. Patient history also assists in the diagnosis. Viral conjunctivitis is usually transmitted between family members or among school children. Gray elevated avascular areas known as lymphoid follicles may also be present.

Another form of viral conjunctivitis is known as epidemic keratoconjunctivitis (EKC), which initially presents with an acute follicular conjunctivitis, profuse watery discharge, and preauricular adenopathy. EKC usually clears within 7–14 d without treatment.

Treatment of nonspecific viral conjunctivitis is largely supportive and requires no drug therapy. Topical vasoconstrictors may provide symptomatic relief, and they may decrease conjunctival injection. If the corneal epithelium becomes compromised and there is a risk for secondary infection, prophylactic antibiotics may be indicated.

A more serious form of viral conjunctivitis is that caused by herpes simplex. Herpes simplex keratoconjunctivitis can occur without any other sign of a herpetic infection. Herpetic lesions often are associated with a neuralgic type of pain that can be excruciating. The pain may be present days before the lesions appear. Again, the absence of pruritus should lead the clinician away from a diagnosis of allergic eye disease. Other classic signs of herpes keratitis include photophobia and a corneal dendritic pattern with fluorescein staining, indicating a corneal ulcer. Herpes keratitis is treated with antiviral agents and/or corneal debridement. Secondary inflammation may leave the cornea scarred and result in a loss in vision. The possibility of herpes keratitis is one of the most compelling reasons to do a thorough slit lamp exam of the anterior chamber with fluorescein staining on all patients with a suspicious red eye or ocular pain.

Inclusion Conjunctivitis

Inclusion conjunctivitis is most commonly found in patients who asymptomatically harbor the chlymidal agent in the genital tract. Common findings of inclusion conjunctivitis include a mucopurulent discharge and a follicular conjunctivitis lasting for more than 2 wk. A Giemsa stain of a conjunctival scraping may reveal intracytoplamic inclusion bodies and will assist in confirming the diagnosis.

Treatment of inclusion conjunctivitis should be aggressive, since there is the potential for the cornea to perforate in a short period of time. Both topical and systemic antibiotics should be used. The patient should be evaluated for other sexually transmitted diseases. Topical tetracycline and oral tetracycline can be used. Doxycycline is preferred by some because of better compliance with its b.i.d. dosing.

Bacterial Conjunctivitis

The most common causes of bacterial conjunctivitis in the noncompromised host are *Staphlococcus* and *Streptococcus*. Bacterial conjunctivitis usually presents with beefy red conjunctival injection as opposed to the pink color associated with allergic conjunctivitis. Also, in conjunctivitis of bacterial origin, there is often a purulent discharge, some pain, photophobia, and possibly foreign body sensation (Fig. 4). Itching is not common with bacterial conjunctivitis. The presence of a purulent discharge and the absence of itching should indicate bacterial conjunctivitis.

Treatment of bacterial conjunctivitis depends on the most likely infecting organism, patient compliance, and cost of the medication. In general, a topical, broad-spectrum antibiotic, such as sulfacetamide, erythromycin, or a combination of

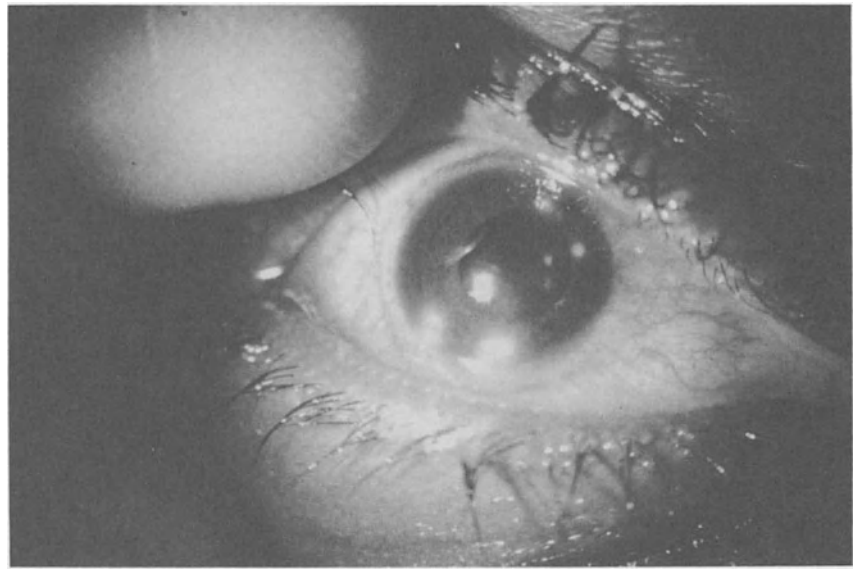

Fig. 4. Bacterial conjunctivitis most likely owing to *Staphylococcus*. Notice the purulent discharge. Photograph courtesy of Barbara Jennings.

polymyxin B, bacitracin, and neosporin, is appropriate. Cultures are indicated if the conjunctivitis is severe. The patient should be followed carefully to ensure that the eye improves. Topical gentamicin and tobramycin are indicated if gram-negative organisms are suspected or seen on gram stain. It should be noted that all of these antibiotics have the potential to elicit an allergic reaction. A careful history for drug allergies, a time limit for therapy, and re-evaluation will minimize complications. Topical ciprofloxacin or ofloxacin offers coverage for a wide spectrum of infecting agents, but should only be used when there is the likelihood for therapeutic failure or the conjunctivitis is thought to be owing to multiple infecting organisms or *Pseudomonas sp.* A partial listing of topical antibiotics is found in Table 6.

Dry Eye Conditions

The health of the anterior segment of the eye is dependent on adequate tear flow. Tears deliver oxygen and other nutrients to the cornea, remove debris, and are vital for ocular lubrication and the overall health of the corneal and conjunctival surface. A decrease in the tear volume or a disruption in the tear layers can lead to dryness, which in turn produces inflammation and predisposes the ocular surface to irritation from allergens. There are many etiologies for dry eye conditions. A few of them are listed below.

Anticholinergic Medications

Chronic use of anticholinergic medications can lead to dry eye symptoms because of decreased lacrimation. Many drugs have antimuscarinic properties, including the first-generation antihistamines, phenothiazines, tricyclic antidepressants, atropine, and scopolamine.

Table 6
Examples of Topical Antibiotics and Antibiotic/Corticosteroid Combinations

Drug	*Concentration*	*Brand name*	*Available size/dose*
Bacitracin	500 U	Baciguent Ophthalmic, AK-Tracin	3.5 and 1 g oint. ½ in. every 3–4 h
Bacitracin and polymyxin B	500 U 10,000 U	Polysporin	3.5 g oint. ½ in. every 3–4 h
Bacitracin and polymyxin B and neomycin	400 U 10,000 U 0.35%	Neosporin®	7.5 mL, 1–2 drops every 3–4 h 3.5 g oint. ½ in. every 3–4 h
Chloramphenicol	0.5%, 1%	Chloroptic®	7.5, 15 mL, 2 drops every 3 h for 48 h
Chloramphenicol	10 mg/g oint.	Chloromycetin®	3.5 g oint. ½ in. every 3–4 h for 48 h
Chloramphenicol and polymyxin B sulfate	10 mg/g 5000 U	Chloromyxin	3.5 g oint, every 3h for 48 h
Chlortetracycline	10 mg/g	Aureomycin	3.5 g oint. ½ in. every 2 h
Ciprofloxacin	0.3%	Ciloxan	2.5, 5 mL, 1–2 drops every 2 h while awake for 2 d, 1–2 drops every 4 h while awake for 5 d
Erythromycin	5 mg/g oint.	AK-Mycin	3.5 and 1 g
Gentamicin	0.3%	Genoptic, Garamycin	1, 5 mL 1–2 drops every 4 h up to 2 drops every 2 h
Gentamicin	3 mg/g	Garamycin®	3.5 g oint. ½ in. b.i.d. or t.i.d.
Polymyxin B and oxytetracycline	10,000 U 5 mg/g	AKTetra	3.5 g oint. ½ b.i.d.-q.i.d.
Sulfacetamide	10, 15, 30%	Bleph-10	2.5, 5, 15 mL, 1–2 drops every 2 h
Sulfisoxazole	4%	Gantrisin	3.5 g oint., ½ in. b.i.d. and every hour of sleep ½ oz. soln., 2–3 drops t.i.d.
Sulfacetamide and phenylephrine	15% 0.125%	Vasosulf	5, 15 mL, 1–2 drops q 2–3°
Tetracycline	1%	Achromycin	0.5, 4 mL, 2 drops b.i.d.–q.i.d.
Tetracycline	10 mg/g	Achromycin	3.5 g oint., ½ in. every 2 h
Tobramycin	0.3%	Tobrex	5 mL, 1–2 drops every 4 h
Tobramycin	3 mg/g	Tobrex	3.5 g oint ½ in. b.i.d.-t.i.d.

Table 6 ***(continued)***

Antibiotic/steroid combinations

Dexamethasone alcohol 0.1% + neomycin 0.35% + polymyxin B 10,000 U (Maxitrol®, Dexacidin®); this combination also available with 0.05% dexamethasone. 3, 5 mL, 3.5 g ointment

Dexamethasone alcohol 0.1% + neomycin 0.35% (NeoDecadron®, AK NeoDex®); also available with 0.05% dexamethasone, 5 mL

Dexamethasone alcohol 1% + tobramycin 0.3% (Tobradex®); also available with 0.05% dexamethasone, 2.5, 5 mL

Dexamethasone phosphate 0.1% + neomycin sulfate 0.5% + Polymyxin B (10,000 U) (Dexacidin®, AK-Trol®) 2, 5 mL

Fluorometholone 0.1% + sulfacetamide 10% (FML-S) 5, 10, 15 mL

Hydrocortisone 1% + neomycin 0.5% + polymyxin B 10,000 U (Cortisporin®) 5, 7.5 mL

Hydrocortisone 1% + bacitracin 400 U + 0.35% neomycin + polymyxin B 10,000 U (Cortisporin) ⅛ oz. ointment

Hydrocortisone acetate 0.5% + chloramphenicol 0.25% (Chloromycetin-Hydrocortisone®) 5 mL

Hydrocortisone acetate 0.5% + neomycin sulfate 0.5% (NeoCortef®) 5 mL

Hydrocortisone acetate 1.5% + neomycin sulfate 0.5% (AK-Neo-Cort®)—also available in hydrocortisone 0.5% 5 mL

Prednisolone acetate 0.2% + sulfacetamide 10% (Blephamide®) 2.5, 5, 10 mL, 3.5 g ointment

Prednisolone acetate 0.25% + 10% sulfacetamide (Isopto Cetapred®) 5, 15 mL, 3.5 g ointment

Prednisolone acetate 0.25% + neomycin sulfate 0.5% (Neo-Delta-Cortef®) This combination also available with 0.5%, prednisolone acetate and 0.25% prednisolone phosphate (Neo-Hydeltrasol®), 5 mL

Prednisolone sodium phosphate 0.25% + sulfacetamide 10% (Vasocidin); also available in a 0.5% + 10% combination (Vasocidin®, Sulphrin®, Metimyd®) 5, 10 mL

Prednisolone acetate 0.5% + neomycin –.35%, polymyxin B 10,000 U (Poly Pred®) 5, 10 mL

Prednisolone alcohol 0.5% + chloramphenicol 1% (Chloroptic-P®) 2.5, 7 mL, 3.5 g ointment

Prednisolone acetate 1% + gentamicin 0.3% (Pred-G®) 2, 5, 10 mL

Proptosis

Eyes that protrude past the capacity for the lids to close can become extremely dry. Without proper lubrication and protection, vision loss can result. One of the most common conditions causing proptosis is Graves Opthalmopathy with or without hyperthyroidism. Symptomatic treatment includes ocular lubricants, especially at night. The underlying cause of proptosis should be defined.

Keratoconjunctivitis Sicca

Keratoconjunctivitis sicca describes a syndrome of profound dry eye. Without an adequate tear volume, the ocular surface is chronically irritated and becomes at risk for in-

fection, scarring, and loss of vision. There are multiple etiologies for keratoconjunctivitis sicca, including advanced age, drugs, and underlying disease states, such as connective tissue diseases, for example, Sjörgen's syndrome. Keratoconjunctivitis sicca seems to be more prevalent in postmenopausal women than in men. Drugs associated with a sicca syndrome include the retinoids, β-blockers, antihistamines, chemotherapeutic agents, and anticholinergic agents.

Symptoms of keratoconjunctivitis sicca begin insidiously, and frequently are attributed to an allergic or infectious process. Mild conjunctival injection, irritation, photophobia, and mucoid discharge are common clinical findings. Corneal epithelial damage is revealed with either fluorescein or rose bengal staining. Treatment includes addressing the underlying pathology, discontinuing the offending drug if possible, and the generous use of artificial tears or ocular lubricants. For severe symptoms, the insertion of punctal plugs may be indicated.

OCULAR PHARMACOKINETICS

There are many factors that contribute to the therapeutic and adverse effect produced by ocularly administered drugs. These include the chemical properties of the drug, the drug formulation, administration technique, and the integrity of the ocular surface. The various components that impact ocular delivery of drugs or adverse effects from ocularly administered drugs are described below.

Tears

The normal tear volume is 8–10 μL, including the fluid trapped in the folds of the conjunctiva. Ocular drugs are usually administered in a 20–25-μL drop. The amount of ocularly administered drug that reaches the systemic circulation is increased with drop size and lipid solubility. The nasolacrimal duct and spillage over the lid margin rapidly removes the excess drug. The drug can be absorbed into the systemic circulation through the nasal mucosa, from swallowing the drug, or from absorption through the conjunctival vasculature.

The normal tear flow rate is 0.5–2.2 μL/min. The concentration of drug available in the tears for absorption by the cornea is inversely proportional to the tear flow. The flow rate and tear volume influence, in part, drug absorption by the anterior segment of the eye.

Cornea

The cornea is a five-layered, avascular structure that functions as the major barrier to ocular drug penetration. It is also the major site of absorption for topically applied drugs. The epithelium and stroma are depots for liphophilic and hydrophilic drugs, respectively.

Liphophilic drugs readily enter the epithelium since its barrier is the plasma membrane. Because the epithelium contains more than two-thirds of the plasma membrane mass of the cornea, it is the most significant depot for liphophilic drugs. If the epithelium is irregular or damaged in any way, drug penetration is enhanced.

The corneal stroma is the major depot for topically applied hydrophilic drugs and the keratocytes presumably provide a reservoir for liphophilic compounds. Because the corneal endothelium is thin, it does not function as a drug storage reservoir.

Sclera and Conjunctiva

The sclera is a vascular structure continuous with the cornea at the limbus. The conjunctiva is also a vascular tissue. Drug absorption into the eye and the systemic circulation can occur through the conjunctiva and the sclera because of the extensive vascularization of these tissues. The conjunctival sac is a large area and its surface can be a major depot for some drugs that are superficially absorbed and then rereleased in the tears. Drug suspensions and ointments allow active drug to dissolve slowly from the conjunctival sac and saturate the tears. In some instances, subconjunctival injections can be given.

Iris

The pigment granules of the iris epithelium absorb both light and liphophilic drugs. Drug binding is reversible, and the iris can function as a drug reservoir. Drug binding by the pigment granules can prevent or delay a single dose of drug from reaching a therapeutic level within the eye.

Aqueous Humor

Drugs absorbed through the cornea can leave the aqueous humor and enter into the general circulation through the canal of Schlemm or through the walls of the iris or other tissues comprising the margins of the anterior chamber.

Ciliary Body

The ciliary body produces the aqueous humor and is a source of drug storage and removal. Located in the ciliary body are metabolic enzymes that perform mostly phase II reactions and melanin granules that can store liphophilic drugs. The ciliary body has no tight junctions to limit the diffusion of drugs or proteins. Drug passage is limited by the apical tight junctions of the nonpigmented cells at the paired layers making up the ciliary epithelium. The uveal circulation rapidly removes these conjugated products from the eye.

Crystalline Lens

The anterior lens epithelium is the most prone to damage from drugs or toxic substances. Hydrophilic drugs or those with a large molecular size cannot be absorbed by the lens owing to the epithelial barrier. Lipid-soluble drugs can pass slowly into and through the lens cortex. Removal of the lens, such as that for cataract surgery, alters the kinetics between aqueous and vitreous humor.

Vitreous Humor

The vitreous can serve as a major reservoir for drugs as well as a temporary storage depot for metabolites. Most low-molecular wt substances diffuse into the vitreous from the ciliary body and the aqueous humor. Hydrophilic drugs have a prolonged half-life in the vitreous humor and can be eliminated from the eye by crossing the lens into the aqueous humor where they are excreted through the aqueous outflow pathways.

Retina and Optic Nerve

There is a barrier in the retina similar to the blood–brain barrier. This barrier (the blood–retinal barrier) protects the eye against the entry of a wide variety of systemic

drugs and/or metabolites and toxins. Lipophilic drugs cross the barrier easily in either direction.

Routes of Administration

In general, the most common route of administration of a drug for ocular use is via drops, solutions, or ointments that are applied directly to the ocular surface. Ocular administration of drugs is a noninvasive method of drug administration that offers several advantages, such as ease of administration, rapid delivery and absorption of the drug to the site of action, and a decreased risk of adverse systemic effects. The effect of a topical eye drop is dependent on:

- The size of the drop;
- The volume of the conjunctival sac;
- The underlying health of the corneal epithelium;
- Patient compliance; and
- The technique used when administering the drop.

The average volume of an ophthalmic drop is approximate to the total volume of the conjunctival sac. In general, the conjunctival sac contains 10 μL of tears, and adding additional volume from an ophthalmic drop exceeds the capacity. Excess fluid will spill over the edge of the lid or will be drained via the punctum into the nasolacrimal system. Absorption of any ocularly administered drug through the nasal or pharyngeal mucosa has the potential to produce adverse systemic effects and should always be considered.

Ocularly administered drugs have the potential to produce ocular irritation and reflex tearing. This excess tearing will dilute and facilitate the elimination of a topically administered drug, thereby decreasing its therapeutic effect. Much of the drug may spill over the lid margin, become deposited onto the eyelashes, or may be lost to punctal drainage. To some extent, the formulation of the drug can determine the ocular penetration, contact time, and therapeutic effect. Drugs formulated into viscous preparations, such as ointments, gels, and lipid soluble drops, have a longer contact time with the ocular surface and provide a greater absorption of the drug into ocular tissues. Drug loss and the risk for systemic effects from an ocularly administered drug can be minimized by careful selection of the drug formulation and proper instillation techniques, which are described in Table 7.

The underlying health of the corneal epithelium determines the extent to which an ocularly administered drug will be absorbed into the anterior and posterior structures of the eye. Since most ocular allergic conditions affect the conjunctiva, increased drug penetration into the cornea has the potential to decrease the therapeutic effect. The ocular penetration of any drug is enhanced when the corneal epithelium is inflamed, irregular, traumatized, or ulcerated.

Ocular Drug Formulations

Solutions and suspensions are the most common formulation of ocular medications. As with other medications, ocular drugs contain inactive ingredients. These include

preservatives, agents to increase viscosity, antioxidants, wetting agents, buffers, and agents to adjust tonicity.

Preservatives control growth of microorganisms that may be introduced into the solution accidentally. Examples of common ophthalmic preservatives are listed in Table 8. Some of these agents can stain contact lenses or have a high incidence of hypersensitivity reactions.

Ocular ointments are ideal for prolonged contact time of the drug with the eye. Ointments can cause blurry vision; the patient should be informed of the possibility of a temporary decrease or blurring of vision. Drugs formulated into ocular gels also serve as vehicles for prolonged contact time of the drug with the eye.

Sometimes the use of multiple ocular mediations is necessary. In this instance, drops should be administered no less than 5 min apart to allow for adequate drug–tissue contact time and to prevent one drug from diluting the other. When using an ointment and solution, apply the solution before the ointment, since it can retard the entry of subsequent ocular drops.

Drugs Used in the Treatment of Ocular Allergic Disorders

Treatment of ocular allergies is largely based on the severity of symptoms. A suggested treatment regimen is listed in Table 9. Topical agents provide the easiest and most direct route for placing a drug at the affected tissue. There are several topical agents available for the treatment and, to some degree, the prophylaxis of ocular allergies. These include vasoconstrictors, antihistamines, mast cell stabilizers, and anti-inflammatory agents. Efficacy of these agents varies from patient to patient, and choice of agent used will depend on the underlying health of the eye and other variables, such as drug cost, contact lens wear, and potential for compliance.

Topical Vasoconstrictors

Vasoconstrictors, such as phenylephrine and tetrahydrozoline, are sympathomimetic agents that decrease vascular congestion and eyelid edema via α-receptor stimulation. They have no effect in diminishing the allergic response. There are several topical vasoconstrictors available. These are listed in Table 10.

Systemic absorption of vasoconstrictors is concentration-dependent. There have been few reports of systemic adverse effects of a 10% solution of phenylephrine when used for induction of mydriasis. These events would not be expected with vasoconstrictors formulated for ocular allergies, since they are used in much lower concentrations. Other adverse effects of topical vasoconstrictors include burning and stinging on instillation, mydriasis, especially in patients with lighter irides, and rebound hyperemia or conjunctivitis medicamentosa with chronic use. Although rare, some vasoconstrictors can be absorbed in sufficient amounts to produce adverse cardiovascular side effects, such as increased blood pressure. These effects usually occur in higher concentrations, but caution is warranted in patients who have poorly controlled hypertension or congestive heart failure.

Although rare, phenylepherine has been shown to produce severe allergic blepharoconjunctivitis that is accompanied by a mucopurlulent discharge. This effect is usually seen several hours after administration and resolves within 3 d after administration.

Table 7
Instillation Techniques for Ophthalmic Pharmaceuticals to Maximize Therapeutic Effect and Decreased Adverse Effects

1. Wash hands.
2. Tilt the patient's head back to a horizontal position, grasp the lower eyelid between the thumb and index finger to form a pocket; and instruct the patient to look up.
3. Gently grasp lower eyelid below eyelashes and pull the eyelid away from the eye to form a pouch.
4. Place dropper directly over the eye, avoiding contact of the dropper with the ocular surface or any other surface.
5. Patient should look up before the drop is administered. Avoid administering drop directly on the cornea. The cornea is densely innervated and drops placed directly on it tend to splash out and are painful. If the drug formulation is stable at 4°C, cold drops may be instilled since the decreased temperature acts as a mild anesthetic and may delay any irritation caused by the eyedrop.
6. After instilling the drop, instruct the patient look downward for several seconds.
7. Bring the lower lid upward until it touches the globe to minimize overflow.
8. Instruct the patient to close his or her eyes gently for 1–2 min. Closing the eyes tightly expels the drug.
9. Apply gentle pressure with the fingers to the bridge of the nose; this occludes the nasal-lacrimal ducts and prolongs drug contact with the eye while minimizing systemic absorption.
10. Do not rub the eye and minimize blinking.
11. Do not rinse the dropper.
12. Avoid using ocular medications that have changed color or are expired.
13. Wait 5 min between drops, especially if more than one medication is being used.

Recommended procedures for the administration of ophthalmic ointments:

1–3. As described above
4. Place a 0.25–0.5 in. strip of ointment in the lower lid.
5. Close the eye gently, and roll eye in all directions for 1–2 min. Temporary blurring of vision is likely.
6. Wait 10 min before applying a second ointment.

Other tips:

1. Systemic absorption of ophthalmic drops can be minimized by compressing the nasal lacrimal ducts for 1–2 min following the instillation of drops. This retards the absorption by the nasal and pharyngeal mucosa and keeps the drug in contact with the ocular surface for a longer period of time
2. Because of the rapid drainage of solutions from the eye and the limited reservoir for additional volume, limit multiple-drop administration to 1 drop every 5 min. This ensures that the first drop is not flushed away by the second or that the drops are not diluted by each other.
3. Topical local anesthetics increase the penetration of drugs to the cornea by decreasing the blink reflex and the production and turnover of tears. Local anesthetics can also diminish the discomfort of other drops that may sting or burn when administered
4. Eyes that have been injured or are lacking the normal barriers, and those patients with chronic dry eye have an increased penetration of ocularly administered drugs and a greater risk for systemic absorption

Table 7 ***(continued)***

5. Ophthalmic suspensions mix with tears less rapidly and remain in contact with the eye for a longer period of time
6. Ophthalmic ointments have the longest drug-ocular surface contact time, but impede the delivery of other ophthalmic agents. They also tend to blur vision and should not be used with contact lenses, or in those patients where clarity of vision is necessary (heavy machinery operators, drivers, and so on); ointments may also impair corneal wound healing

Table 8
Common Ophthalmic Preservatives

Benzalkonium chloride[a]
Cetylpyrinium chloride
Chorobutanol
EDTA
Mecurial preservatives (thimerosal[b])
Methyl and propylparabens
Phenylethyl alcohol
Sodium benzoate
Sodium propionate
Sorbic acid

[a]Stain contact lenses and should not be administered with lenses in the eye.
[b]High incidence of allergic reactions.

Table 9
Summary of Treatment Regimens for Ocular Allergies

Symptoms	*Therapeutic agent*
Mild	Cold compresses, ocular wetting solutions or lubricants, topical vasoconstrictor and/or antihistamines, systemic antihistamines
Moderate	Add topical or oral NSAIDS, good lid hygiene
Severe	Add topical or systemic antiinflammatory steroids, antibiotics when necessary for secondary infection
Prophylaxis	Mast cell stabilizers

Topical Antihistamines

Since many of the ocular symptoms of the allergic response are mediated by histamine, histamine antagonists have been one of the mainstays in the treatment of allergic disease. In the eye, histamine is thought to mediate many of the symptoms of allergy by activation of the H_1 receptor (itching) and to some extent, the H_2 receptor (conjunctival injection or vasodilation). Classical antihistamines block the binding of histamine at the H_1 receptor and relieve some of the symptoms of allergies. Topical antihistamines de-

The Topical Preparations for Therapy of Allergic Eye Disease

- Vasoconstrictors;
- Antihistamines;
- Nonsteroidal anti-inflammatory agents;
- Mast cell stabilizers; and
- Costicosteroids.

All of these are safe and can be used by a primary care physician without concern except for corticosteroids. The use of corticosteroids should be under the direction of a primary eye care provider.

Table 10
Ocular Decongestants Used in the Treatment of Allergic Conjunctivitis

Brand	*Drug contents*	*Concentration*	*Dose*
AK-Con	Naphazoline	0.025%	1–2 every 3–4 h
Albalon		0.1%	1–2 every 3–4 h
Clear Eyes		0.12%	1–2 q.i.d.
Naphcon		0.012%	1–2 every 3–4 h
Opcon		0.1%	1–2 every 3–4 h
AK-Nefrin	Phenylepherine	0.12%	1–2 b.i.d. or t.i.d.
Ocugestrin		0.12%	1–2 b.i.d. or t.i.d.
Ocu-phrin		0.12%	1–2 b.i.d. or t.i.d.
Prefrin Liquifilm		0.12%	1–2 q.i.d.
Relief		0.12%	1–2 q.i.d.
Collyrium	Tetrahydrozoline	0.5%	1–2 q.i.d.
Murine Plus		0.5%	1–2 q.i.d.
Soothe		0.5%	1–2 q.i.d.
Visine		0.5%	1–2 q.i.d.

crease itching, lacrimation, and swelling of the periocular tissues. There are several topical antihistamines available for the management of ocular allergies. Some of the individual agents are listed in Table 11. Many agents are combined with topical decongestants for a synergistic effect. Some studies have indicated that antihistamines with decongestants relieve symptoms of ocular allergy better than topical antihistamines alone.

Levocabastine is a newer antihistamine that is chemically unrelated to other H_1 antagonists. In multiple clinical trials, levocabastine was shown to be as effective as chromolyn sodium and other topical antihistamines/vasoconstrictor preparations in preventing and treating seasonal allergic conjunctivitis. Some studies have shown that levocabastine is more effective than chromolyn sodium in allergic prophylaxis. When compared to oral antihistamines, levocabastine was as effective as oral terfenadine, but appeared to be more effective when pollen counts were elevated. For the prophylaxis of ocular allergies, levocabastine was superior to mast cell stabilizers, since the effect was seen within minutes of application vs the days to weeks necessary for the mast cell stabilizers to produce a clinical effect.

Table 11
Topical Antihistamines

Brand	*Drug contents*	*Concentration*	*Dose*
Albalon-A Vasocon-A	Antazoline, naphazoline	0.5%, 0.05%	1–2 every 3–4 h
Prefrin-A	Pyrilamine, phenylephrine	0.1%, 0.12%	1–2 every 3–4 h
Naphcon-A AK-Con-A Opcon-A	Pheniramine, naphazoline	0.3%, 0.025%	1–2 every 3–4 h
AK-Vernacon	Pheniramine, phenylepherine	0.5%, 0.125%	1–2 every 3–4 h
Livostin	Levocabastine	0.05%	1 b.i.d. or q.i.d.

Levocabastine is systemically absorbed after ocular administration. However, plasma levels are in the ng/mL range and are not of significance. Adverse effects associated with levocabastine include transient burning and stinging, and headache. No CNS or cardiovascular effects have been reported after ocular administration.

Pheniramine and pyrilamine are two other antihistamines available for the topical treatment of ocular allergies. Both are available in combination with vasoconstrictors. There have been no studies that have indicated that either has a greater clinical efficacy.

In general, topical antihistamines can be irritating when administered to the eye. With prolonged use of topical antihistamines, there is the risk of developing sensitivity reactions that can further aggravate ocular allergies. For antihistamines that are nonselective and block muscarinic receptors in addition to H_1 receptors, ciliary muscle paralysis, mydriasis, and photophobia may result. This effect is more pronounced in patients with lighter irides. Also related to muscarinic receptor blockade is the risk for angle closure glaucoma, especially in patients with a history of narrow-angle glaucoma and those with narrow angles. The mydriatic effect causes the anterior chamber to become more shallow, and there is also a decrease in aqueous humor outflow leading to rises in IOP. The classic signs of acute angle closure glaucoma include headache, blurry vision, nausea and vomiting, and changes in corneal opacity.

Topical NSAIDS

There is only one topical preparation of a nonsteroidal anti-inflammatory agent (NSAID) ketorolac (Accular®, 0.5%), available for the management of allergic conjunctivitis. It has been shown to be efficacious for the management of itchy, watery eyes and to improve contact lens intolerance owing to allergies. As an NSAID, ketorolac inhibits prostaglandin formation in the eye and decreases ocular itching. Although several other NSAIDS are available for ophthalmic use, ketorolac is the only one approved for the management of allergic conjunctivitis.

In placebo-controlled studies, ketorolac consistently improved the ocular inflammation and itching associated with allergic conjunctivitis. Systemic absorption of the drug after ocular administration is negligible. Because Accular® is preserved with BAK, it should not be administered when contact lenses are in the eye. Adverse effects associated with ketorolac include burning and stinging on instillation, allergic reactions, and transient conjunctival hyperemia.

There are currently no other topical NSAIDS approved for use in allergic eye disease. A topical formulation of indomethacin has been evaluated for its efficacy in the treatment of vernal conjunctivitis with good results, and other topical NSAIDS will most likely be available in the future.

Topical Mast Cell Stabilizers

Mast cell stabilizers, when used prophylactically, prevent the degranulation of mast cells by inhibiting calcium influx and thus the release of allergic mediators. They may also have other mechanisms that have not yet been elucidated. These drugs are effective as prophylactic agents only; they do not inhibit the allergic response once it has begun. There are currently two mast cell stabilizers available for the treatment of ocular allergies; lodoxamide (0.1%) and chromolyn sodium (4%). Nedocromil (2%) has also been formulated for ocular use, but is not available in the United States.

Clinical trials with chromolyn sodium, now remarketed in the United States, indicate that it is effective in decreasing the symptoms of allergic conjunctivitis when used prophylactically, i.e., before exposure to the allergen. Improvement of symptoms can occur within 10 d after regular treatment has begun. There is no systemic absorption of the drug owing to its lipid insolubility. Irritation and burning with instillation are the most common adverse effects associated with chromolyn sodium.

Nedocromil also inhibits the degranulation of mast cells. It appears to be more potent than chromolyn and has the added benefit of inhibiting the activation of various inflammatory cells, such as eosinophils, macrophages, and neutrophils. It may also decrease the migration of inflammatory cells. In clinical trials, a 2% solution of nedcromil effectively decreased the symptoms associated with seasonal allergic conjunctivitis. It does not appear to be any more effective than chromolyn in controlling symptoms, but may have better compliance since it is administered twice daily compared to chromolyn, which is administered four times per day. Adverse effects reported include transient burning and stinging, and conjunctival hyperemia.

Clinical trials indicate that lodoxamide is as effective and, in some cases, more so than chromolyn sodium in reducing the itching, tearing, and general discomfort associated with allergic conjunctivitis. Lodoxamide is also more effective than chromolyn in reversing the corneal complications of vernal conjunctivitis. When lodoxamide was used chronically by vernal conjunctivitis patients, corneal epithelial defects resolved, and papillae, hyperemia, and conjunctival discharge were also diminished.

Mast cell stabilizer use in vernal conjunctivitis is effective in reducing some of the symptoms, such as pruritus and chemosis. In clinical trials, nedocromil and chromolyn sodium were equally efficacious.

For the best clinical result, all mast cell stabilizers must be used on a regular, prophylactic basis to be effective. Systemic absorption of lodoxamide after ocular administration has been shown to be negligible, and it appears to be safe in children older than 2 yr of age. One to two drops of lodoxamide should be administered four times a day before exposure to the allergen. The safety of the lodoxamide when used for longer than 3 mo has not yet been shown in controlled clinical trials.

Topical Corticosteroids

Corticosteroids are used for acute inflammatory conditions of the eye, such as severe allergic conjunctivitis, acne rosacea, superficial punctate keratitis, iritis, and corneal in-

jury from chemical, thermal, or radiation exposure. These drugs are the gold standard as anti-inflammatory agents. Glucocorticoids block the production of both prostaglandins and leukotrienes by stimulating the formation of macrocortins, which inhibit the enzyme phospholipase A_2. Because their mechanism of action involves protein synthesis, onset of action is delayed by several hours. Glucocorticoids inhibit both the early and late phase of the allergic response.

As with the systemic preparations, steroids should be used in the lowest dose possible for the shortest time. It is best to taper the dose rather than to discontinue abruptly. Ocular formulations include suspensions, solutions, and ointments.

There are differences in individual drug anti-inflammatory actions owing to differences in the corneal penetration. Acetate and alcohol preparations are more hydrophobic and have better corneal penetration. All those formulated as phosphates are less likely to penetrate the cornea. Individual agents are listed in Table 12.

Because of the propensity for adverse effects, the use of corticosteroids in allergic eye disease remains controversial. Many clinicians believe that these drugs should not be used without a consultation from an ophthalmologist.

Prolonged use of a topical steroid results in an increased risk for ocular infection, cataracts, increased intraocular pressure, glaucoma, corneal perforation, and vision loss. Elevated intraocular pressure appears to be genetically determined, and the magnitude of pressure elevation is directly related to the concentration of the drug, frequency of use, and duration of therapy. With prolonged elevation in intraocular pressure, irreversible glaucomatous changes and vision loss can result.

The mechanism of glucocorticoid-induced cataracts is not well known, but there is a positive correlation between length of therapy and dose in the development of the opacities. Corticosteroids affect the water transport processes in the lens, an event that may increase lenticular permeability to cations. Normal water and electrolyte transport is necessary to maintain the transparency of the lens. Some animal and in vitro studies have suggested that glucocorticoids may alter the lens proteins in such a manner that causes cross linking or changes the structure, so that the lens is more susceptible to oxidation and ultimately transparency loss.

These drugs should not be used in most active infections, unless the underlying infection is being treated concurrently. Chronic, long-term use of topical steroids predisposes the patient to cutaneous infection with skin flora, fungus, and the herpes virus.

For those patients for whom chronic corticosteroid therapy is necessary (>10 days), it is advisable to monitor patients frequently and carefully for the development of adverse effects. Although the changes in the opacity of the lens are not reversible, they can be prevented by careful monitoring and discontinuing the drug.

Local Anesthetics

Topical anesthetics are useful for alleviating acute pain, assisting in determining the etiology of ocular pain, and performing certain surgical procedures. One or two drops of local anesthetics can be invaluable in alleviating severe discomfort from ocular allergies and will allow the patient to open his or her eyes for examination. This tactic is used especially in emergency departments when pain and photophobia from severe ocular allergies and ocular trauma are present.

Local anesthetics are drugs that block nerve conduction when applied locally in appropriate concentrations. They prevent the generation and the conduction of nerve im-

Table 12
Ocular Preparations of Corticosteroids

Drug	*Concentration dose*	*Brand name*	*Preservative*
Dexamethasone-phosphate	0.1%	Decadron	BAK
Fluorometholone-polyvinyl alcohol	0.1%, 0.25%	FML, Fluor-Op FML Forte	BAK BAK
Medrysone-polyvinyl alcohol	1%	HMS Liquifilm	BAK
Prednisolone acetate	0.12% 1%	Pred-Mild Pred-Forte	BAK BAK
Prednisolone sodium-phosphate	0.125% 1%	Econo-Pred Inflamase Forte	BAK BAK

[a]Dexamethasone, prednisolone, and fluorometholone are available in combination with antibiotics. Prednisolone acetate is the most efficacious for treating corneal inflammation. Medrysone has the least incidence of raising intraocular pressure.

pulse by decreasing or preventing sodium influx into the neuronal membrane. This action is the result of their direct interaction with voltage-sensitive Na^+ channels. They bind to specific receptors that control the gating of Na^+ channels. They act on any part of the nervous system and on every type of nerve fiber. Their action is reversible, and their use is followed by complete recovery in nerve function with no evidence of structural damage to nerve fibers or cells.

The degree of block produced by a given concentration of local anesthetic depends markedly on how much and how recently the nerve has been stimulated. A resting nerve is much less sensitive to a local anesthetic than one that has been recently and repetitively stimulated.

The active site for local anesthetics is the inner portion of the neuronal membrane. Local anesthetics are weak bases, crossing cell membranes readily at physiological pH. Once inside the neuronal membrane, they become ionized and active. Local anesthetics are not effective in infectious tissues, because the low pH of pus and other cellular debris alters their pharmacokinetics.

Local anesthetics are categorized based on their chemical structure. There are two main classes, the esters and the amides. Ester-local anesthetics include cocaine, procaine, proparacaine, tetracaine, and benzocaine. Lidocaine, bupivacine, and mepivacaine are examples of amide-local anesthetics. Specific agents are listed in Table 13.

The ester local anesthetics are metabolized by plasma cholinesterases and the liver. The amides are degraded by the liver. The toxicity of the local anesthetics depends on rate of absorption and rate of destruction.

All of the local anesthetics are associated with stinging and burning on instillation and conjunctival injection. Chronic use causes a loss of duration of anesthesia, epithelial erosion, keratitis, corneal opacification, and scarring and impaired wound healing. Local anesthetics should never be dispensed to the patient. Several patients have lost their vision because local anesthetic was dispensed to them for PRN use. Systemic absorption of topically administered drugs, although rare, can produce CNS excitation, followed by depression, cardiovascular collapse, and death. CNS stimulation with ocular administration of cocaine is also possible.

Table 13
Agents Commonly Used for Ocular Anesthesia

Drug	*Onset*	*Duration*	*Dose*
Tetracaine 0.5% (Pontocaine®)	10–20 s	20 min	1–2 drops
Proparacaine 0.5% (AK-Taine, Ophtaine®)	10–20 s	20 min	1 drops
Cocaine 4%, 10%	5 min	2 h	1 drops

Hypersensitivity to local anesthetics is rare. It may manifest as dermatitis, asthma, or anaphylaxis. Hypersensitivity occurs most frequently with the ester types. Proparacaine has the least incidence of crossreactivity with any other local anesthetic.

Topical anesthetics are contraindicated in patients with known hypersensitivity. The patient should avoid rubbing or touching the eye or reinserting contact lenses until sensation has returned to the eye.

SYSTEMIC AGENTS FOR THE TREATMENT OF OCULAR ALLERGY

Antihistamines

Although not the sole mediator of the allergic response, histamine mediates many of the signs and symptoms through both H_1 and H_2 subtypes of receptors. H_1 receptor antagonists were introduced into therapeutic use five decades ago. Binding of the H_1-antagonist to the H_1-receptor does not produce a response, but rather, blocks the actions of endogenous histamine at the receptor. For the most part, H_1 antagonist binding is competitive and reversible, with the notable exception of astemizole.

H_1 antagonists are well absorbed after oral administration and generally have an onset of action within 30 to 60 min with an average duration of action between 3 and 6 h. Exceptions are meclizine, terfenadine, and mequitazine, which have durations of action of 12–24 h. Astemizole has an active metabolite with a half-life of up to 100 h. Older, first-generation antihistamines distribute in total body water and readily cross the blood–brain barrier. The newer second-generation agents (astemizole, terfenadine, and loratadine) do not enter the CNS and may not penetrate the eye well. The H_1 antagonists are summarized in Table 14. Some of the antihistamines have nonhistaminergic effects, and may block the formation or actions of other inflammatory mediators or stabilize mast cells.

Classical antihistamines are rather nonselective antagonists in that they have varying abilities also to antagonize muscarinic cholinergic receptors, α-adrenergic receptors, and serotonergic receptors. Newer agents, collectively referred to as second-generation H_1 antagonists, by virtue of not crossing the blood–brain barrier and being more selective for H_1 receptors, are associated with fewer undesired side effects. Frequent side effects of H_1 antagonists are essentially caused by their anticholinergic actions, and include dry mucous membranes, blurred vision, dysuria or urinary retention, tachycardia, mydriasis, and constipation. Central nervous system side effects range from sedation to insomnia, restlessness, tremors, and euphoria. Generally, both anticholinergic and CNS side effects are much less frequent and pronounced with the second-generation antihistamines.

Table 14
Second-Generation H_1 Receptor Antagonists

	Onset of action	*Duration of antihistaminergic effect*
Astemizole	24–48 h	4–6 wk
Azatadine	1–2 h	8–12 h
Azelastine	1–2 h	24 h
Citirizine	1–2 h	24 h
Loratadine	1 h	12–24 h
Rocastine	15 min	4–8 h
Setastine	1–2 h	16 h
Terfenadine	1–2 h	12–24 h

Systemic Corticosteroids

For severe exacerbations of ocular allergies, a course of systemic corticosteroids may be indicated. As mentioned previously, corticosteroids inhibit the allergic response by blocking the production the mediators of the allergic response. Prednisone is the most common systemic corticosteroid used for acute exacerbation of allergic disease.

Corticosteroids are associated with predictable adverse effects that are dependent on both the dose and more importantly, on the duration of therapy. Steroids used for short periods of time (< 7–10 d) are associated with very little risk, even when used in relatively large doses. With long-term administration, corticosteroids produce a net retention of sodium and water, edema, increased blood pressure, hyperglycemia, increased risk for infection, osteoporosis, cataracts, increased intraocular pressure with glaucomatous changes, and a Cushinoid state. Long-term use of corticosteroids should be reserved for sight-threatening diseases. They should be used with caution in patients with underlying cardiovascular disease and diabetes.

Ocular Allergy and Contact Lens Use

There are well over 20 million patients who wear contact lenses, and with the frequency of allergic disease, many of these suffer from at least seasonal allergies, including conjunctivitis. There is no set rule about allergy patients and contact lens wear, since the underlying health of the eye and the patient's ability to tolerate the lens greatly determines wear. There are, however, some absolute contraindications for contact lens wear in allergy patients.

Patients with AKC should not wear contact lenses because of the severity of this illness. Also, patients with acute exacerbations of vernal conjunctivitis should not wear contact lenses. Patients with GPC conjunctivitis should refrain from wearing contact lenses, since that is most likely the underlying cause of their conjunctivitis. Often a holiday from lens wear, changing lens polymers, or changing cleaning habits will help in the resolution of the symptoms.

Patient should also not wear their lenses while applying ocular medications for allergies. Many ophthalmic drops contain preservatives that can permanently stain soft contact lenses. Contact lenses can alter the distribution of ocularly administered drugs, thus

greatly decreasing the desired therapeutic effect, or in some cases can concentrate the drug within the lens polymer and result in toxic effects on the corneal epithelium.

There is an inherent risk in placing another potential irritant on the eye, i.e., the contact lens. As long as the patient tolerates wearing the lens without discomfort, most eye care professionals will allow a limited wearing time during exacerbations of allergies.

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12 Urticaria and Angioedema

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CONTENTS

INTRODUCTION

Urticaria and angioedema are the same pathophysiologic process with the variation of clinical presentation between the two resulting from the cutaneous tissue level involved. Urticaria is a well-demarcated skin reaction occurring in the superficial epidermis. The lesions are characterized as erythematous, blanchable, raised lesions that occur and resolve within hours. Occasionally, single lesions will last up to 24 h. Typically the involved skin itches intensely. The raised lesions may vary from 1–2 mm to many centimeters in diameter and usually have serpiginous borders (Fig. 1). Angioedema is a swelling of the deeper cutaneous and subcutaneous tissue with a predilection for the periorbital, perioral, and oral tissues (Fig. 2A, B). The swelling does not itch and resolves over 24–48 h. Individuals experience both conditions in approx 50% of cases, urticaria alone in 40%, and angioedema alone in 10%.

Urticaria and angioedema affect approx 15–20% of the population, with <5% experiencing chronic symptoms. By definition, urticaria and angioedema of duration >6 wk are designated chronic. Chronic urticaria and angioedema are more prevalent in middle-aged adults and females. The natural history of chronic urticaria and angioedema is poorly defined. The chronic condition usually resolves within 1 yr, but approx 10–40% experience exacerbations for a decade or more.

ETIOLOGY AND CLINICAL FEATURES

Etiology

The determination of the etiology is more likely with acute than chronic disease owing to historical identification of causal factors in the former. The more common eti-

From: *Allergic Diseases: Diagnosis and Treatment*
Edited by P. Lieberman and J. Anderson Humana Press Inc., Totowa, NJ

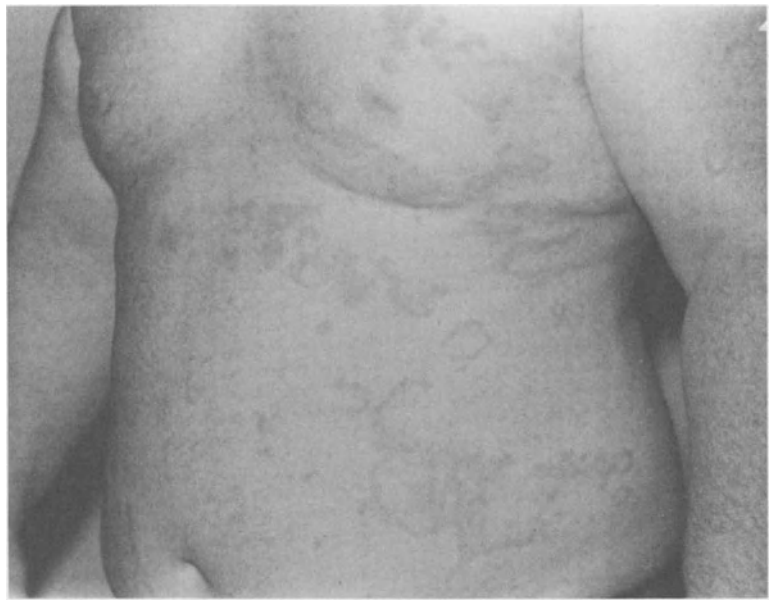

Fig. 1. An urticarial skin lesion demonstrating the typical serpiginous, well-defined border with raised margin. The central clearing often occurs in larger lesions but not as commonly with smaller hives.

Key Features of Urticaria and Angioedema

- Urticaria—erythematous, well-demarcated, highly pruritic lesions usually persisting at same site no longer than a few hours;
- Angioedema—swelling in dermis and subcutaneous tissue, nonpruritic, usually lasting no longer than 48 h;
- Affects up to 20% of population;
- Considered to be chronic if present >6 wk;
- Cause of reactions usually not established, more likely to be found in acute cases; and
- In the vast majority of cases, urticaria and angioedema are not owing to the presence of a systemic illness

ologies of acute urticaria and angioedema include ingested foods, medications, immunotherapy injections, and insect bites or stings. The pharmaceuticals frequently producing urticaria and angioedema are listed in Table 1. Foods most commonly responsible are listed in Table 2. Allergens causing inhalant sensitivity rarely trigger urticaria and angioedema, although cutaneous pollen exposure and animal contact, such as licking by a cat, will occasionally result in reactions in highly sensitive subjects. Dermal contact with latex or methylparaben (a preservative used in topical preparations) is another example of contact urticaria in subjects with specific allergy to these substances. Cinnamaldehyde, a fragrance, is another contact cause of urticaria, but this does not appear to be owing to allergy or IgE antibody specific for the substance. Urticaria and an-

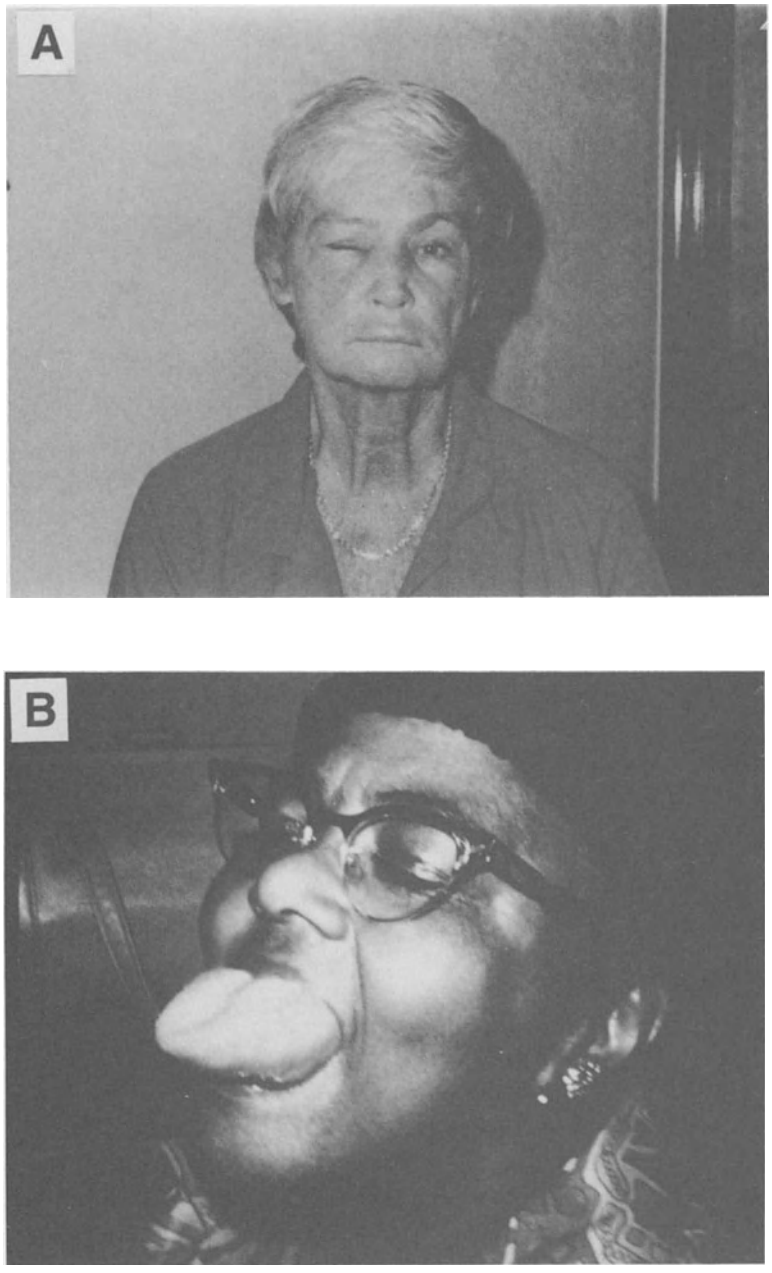

Fig. 2(A) Idiopathic angioedema affecting the periorbital soft tissue. This is a typical area of involvement. Often the swelling occurs during the early morning with the problem identified by the affected subject on awakening. The swelling of idiopathic angioedema usually reaches maximum size within 12 h of onset and resolves over 24–28 h. **(B)** Idiopathic angioedema affecting the tongue. This subject experienced recurrent attacks of swelling localized to the tongue but never experienced airway obstruction or compromised airway. Dramatic soft tissue swelling is characteristic of angioedema and often affects the periorbital tissues, tongue and soft palate, lips, and genitalia. Angioedema secondary to acute allergic reactions, anaphylaxis, hereditary angioedema, and rarely angiotensin-converting enzyme inhibitors may lead to airway obstruction, requiring intubation or tracheostomy.

Table 1
Pharmaceuticals that Commonly Cause Acute Urticaria and Angioedema

β-lactam antibiotics	Radiocontrast agents (particularly high osmolar)
Cephalosporins	Streptokinase
Diuretics	Sulfonamides
Muscle relaxants	Tetracycline
Narcotic analgesics	Tranquilizers
Nonsteroidal anti-inflammatory drugs	

Table 2
Foods Commonly Associated with Urticaria and Angioedema

Egg	Shellfish
Fish	Soy
Milk and dairy products	Tree nuts
Peanut	Wheat

gioedema from insects are the result of local reactions at the site of sting or bite or, less commonly, systemic reactions. The former situation often results in smaller, more persistent hives designated papular urticaria.

The etiology of chronic urticaria and/or angioedema is determined in <5% of cases despite extensive clinical and laboratory investigation in published series. Thus, the usual diagnosis of chronic urticaria and/or angioedema is idiopathic. A review of 1300 cases determined that, when the history did not suggest a cause or an associated medical condition, virtually nothing emerged from subsequent laboratory tests. The potential causes of chronic urticaria and angioedema are listed in Table 3.

The lack of an etiology in 95% of chronic urticaria and angioedema is a frustration for both the affected subject and treating physician. The importance of mediator release from mast cells and basophils in idiopathic urticaria and angioedema is supported by the clinical resemblance to proven allergic forms of urticaria. Increased spontaneous histamine release from peripheral basophils has also been demonstrated in subjects with idiopathic urticaria and angioedema. Monocytes, macrophages, lymphocytes, eosinophils, and other cell types may produce various histamine-releasing factors. One group of investigators has described an autoantibody specific for the high-affinity IgE receptor, found primarily on mast cells and basophils, in the majority of subjects with idiopathic urticaria and angioedema. This antibody induces release of histamine when in contact with mast cells and basophils, resulting in the cutaneous manifestations. Less commonly, antibodies with specificity against IgE have been detected. These antibodies likewise may cause histamine release. Why this autoantibody would result in symptoms and signs primarily limited to the skin is not clear. Autoimmune thyroid disease, with microsomal and/or thyroglobulin autoantibody, has also been associated with urticaria in smaller series. Proof of a relationship between thyroid autoimmunity and urticaria is provided by the clinical improvements with thyroid supplement, even when the affected subject is euthyroid. Relapse with discontinued of thyroid has also occurred. Thus, au-

Table 3
Potential Causes of Chronic Angioedema and Urticaria

Food allergy	Infections
Pharmaceuticals	Bacterial
Antibiotics	Fungal
Anticonvulsants	Parasitic infestations
Antisera	Viral
Aspirin and other NSAIDs	Insect, bites, and stings
Diuretics	Malignancy
Estrogen supplements or oral contraceptives	Lymphoma
Globulin	Myeloproliferative disorders
Hormone therapy	Solid tumors
Insulin	Physical phenomena
Muscle relaxants	Aquagenic
Opiates	Cholinergic
Progesterone supplements	Cold
Sedatives and tranquilizers	Delayed pressure
Thyroid supplements	Dermatographia
Contact sensitivity	Solar
Animals	Vibratory
Food products	Transfusion
Latex	Vasculitis
Plants	
Endocrine disorders	
Hyperthyroidism	
Hypothyroidism	
Thyroiditis	

toimmunity may be responsible for the clinical manifestations in a significant number of subjects with idiopathic urticaria and angioedema.

Pathophysiology

The histology of skin from acute urticarial lesions shows mast cell degranulation, dermal edema, dilated venules and lymphatics, widening of the dermal papillae, separation of the collagen fibrils, and little or no cellular infiltration. Acute angioedema has similar changes located in the deep dermis and subcutaneous tissues. In addition to the changes noted in acute disease, chronic urticaria exhibits an increase in perivascular cellular infiltration. Usually T-lymphocytes are the cell population surrounding blood vessels, but occasionally eosinophils or neutrophils are the predominant cell. It is not clear that the inflammatory cell population remains stable in a given individual or whether the cellular infiltration varies depending on the age of an individual lesion at the time of the biopsy. Chronic urticaria has also been associated with an increase in the number of dermal mast cells. Biopsies from urticarial lesions associated with cutaneous vasculitis will generally show a more intense vascular and perivascular cellular infiltration with RBC extravasation. The cell population in urticarial vasculitis is more likely to be neutrophils if serum complement levels are decreased, and lymphocytes if the complement levels are normal.

Clinical Features

Physical Urticarias

The physical urticarias have distinguishing clinical findings that suggest the diagnosis. Dermatographia, the development of urticaria with stroking of the skin, may occur alone or be associated with idiopathic or other forms of chronic urticaria (Fig. 3). Cholinergic urticaria occurs when core body temperature increases, usually with exercise but also with heat exposure. The hives of cholinergic urticaria typically begin as small, 1–3 mm wheals, with large areas of surrounding erythema. The small wheals may coalesce into larger, more typical hives within minutes to hours. Cholinergic urticaria should be distinguished from exercise-induced anaphylaxis, which also may present with urticaria. Urticaria associated with exercise-induced anaphylaxis is characterized by larger initial lesions, in contrast to the small urticaria of the cholinergic variety. Also, exercise-induced anaphylaxis, in contrast to cholinergic urticaria, does not occur if the core body temperature increases without exercise. Delayed pressure urticaria usually occurs 4–6 h after the application of 10–20 lb or more of weight. This form of physical urticaria and angioedema is associated with arthralgias, myalgias, and malaise. Cold-induced urticaria is readily diagnosed with the application and removal of an ice cube, with urticaria developing in the skin previously in contact with the ice (Fig. 4). Vibratory, aqueous, and UV-dependent urticaria and angioedema occur following exposure to these various physical stimuli. The latter should be distinguished from porphyria.

Urticaria and Angioedema Associated with Other Medical Conditions or Complement Abnormalities

Urticaria is associated with autoimmune diseases. Usually these conditions are evident when subjects present with urticaria and angioedema, although rarely this may be the initial feature of the autoimmune disease. Autoimmune thyroid disease and primary Sjögren's syndrome may be particularly difficult to diagnose at the onset of the urticaria and angioedema. Urticarial vasculitis can usually be distinguished from more benign forms by specific clinical characteristics (Table 4).

A syndrome that could be confused with urticarial vasculitis is episodic angioedema with eosinophilia. This rare condition is characterized by recurrent urticaria and angioedema associated with weight gain owing to fluid retention and generalized edema. Generally, peripheral eosinophilia and an elevation of acute-phase reactants, such as the erythrocyte sedimentation rate, are present. Biopsy of the urticaria or angioedema reveals tissue infiltration with eosinophils with evidence of degranulation. Acute symptoms usually gradually improve over 7–10 d. Systemic glucocorticoid therapy accelerates the improvement.

Urticaria pigmentosa, the most common form of cutaneous mastocytosis, may present initially with urticaria. Individual lesions may be macular, papular, or nodular, usually in a symmetrical distribution. The color is usually reddish brown, and the macules may resemble freckles or lentigo (Fig. 5). Stroking of the skin lesions results in urticaria of the pigmented lesion with intervening erythema (Darier's sign or the "string-of-pearls"). There are other cutaneous manifestations of mastocytosis as well as syndromes with systemic involvement without cutaneous findings.

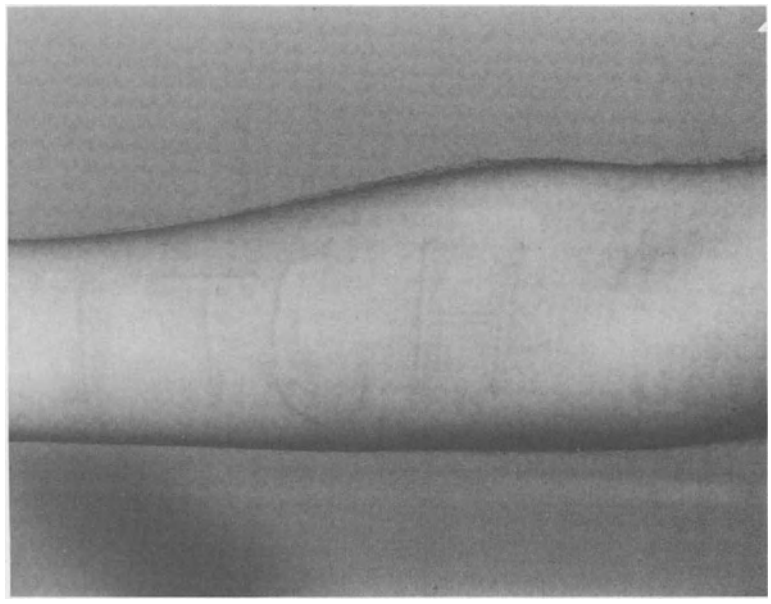

Fig. 3. Linear urticaria resulting from gentle scratching with a blunt object demonstrating the classic "skin writing" of dermatographia. Induced lesions will itch and the resulting rubbing may result in spreading of the urticaria.

Angioedema resulting from angiotensin-converting enzyme inhibitors (captopril, enalapril, lisinopril, benazepril, fosinopril, ramipril) may occur after prolonged treatment or may occur with the first dose. The incidence is 0.1–0.2% of treated subjects. Typically, the angioedema affects the soft tissues of the mouth and throat, and may result in life-threatening airway obstruction. Urticaria is not associated with angiotensin-converting enzyme inhibitor therapy.

The potentially life-threatening angioedema of hereditary angioedema is likewise not associated with urticaria. The angioedema often occurs following trauma. Typically, the swelling is more brawny than the idiopathic variety and persists for 2–3 d or longer. Hereditary angioedema is an autosomal dominant trait with incomplete penetrance. However, despite being congenital, clinical features are often not manifest until adolescence or adulthood and may first develop in late middle-aged or elderly subjects. Family histories are positive in only 40–60% of cases, suggesting spontaneous genetic mutation often occurs. The pathophysiology is associated with a deficiency in the C1-esterase inhibitor protein, a control protein that inhibits the normal, spontaneous activation of C1q. The lack of this negative regulatory protein results in the consumption of C4 both between and during attacks and a decrease in C3 during the development of angioedema. An acquired angioedema, clinically resembling hereditary angioedema, is associated with myelo- and lymphoproliferative disorders. This acquired angioedema is also associated with complement protein abnormalities. In this variety, the C1-esterase inhibitor activity is decreased owing to consumption of the inhibitor by excess activation of C1q. The characteristics of the angioedema are almost identical in these two conditions. The decrease in plasma C1q distinguishes the acquired form from the herditary

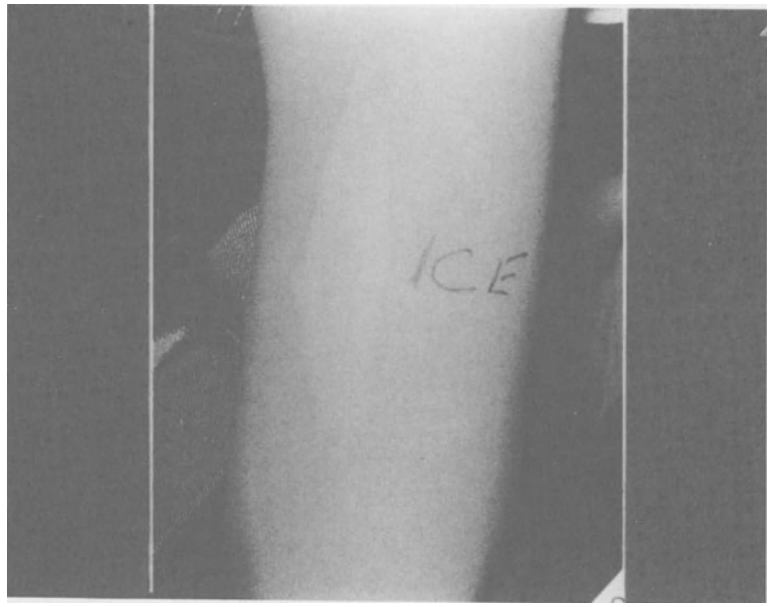

Fig. 4. Urticaria of cold-induced urticaria with the clearly defined margins where an ice cube was applied to the volar aspect of the forearm. Typically the urticaria appears after removal of the ice. Notice where the cold water ran down the arm and induced urticaria.

Table 4
Signs Suggesting Vasculitis as a Cause of Urticaria

Individual lesions lasting longer than 24 h
Livedo reticularis
Purpura, bruising, or petechiae
Dusky discoloration with or without central clearing
Predilection for lower extremities
Systemic symptoms of fever, malaise, arthralgias, myalgias, serositis, or weight loss
Lesions that ulcerate
Symptoms of burning and pain more than pruritus

variety, a distinction that is of significance, since the former is associated with myeloid and lymphoid malignancy.

EVALUATION AND LABORATORY TESTING

History

The most important component of the evaluation of a subject with urticaria and angioedema is a thorough history and physical examination. Specifically, associations are sought with administration of medications, both prescription and over-the-counter, or ingestion of food. Features of other systemic diseases that are linked with urticaria or angioedema are also identified. These include systemic lupus erythematosus, rheuma-

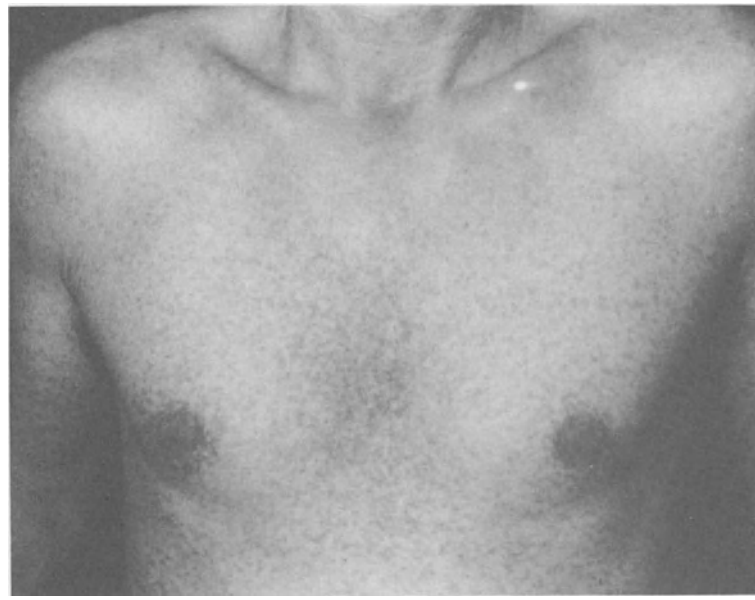

Fig. 5. The lesions of cutaneous mastocytosis may be flat (macular) or raised. The color is often reddish brown and the lesions may appear like lentigo. Skin biopsy of the lesions would confirm the presence of an increase in dermal mast cells.

Key Features of Evaluation

- The history and physical examination are by far the most important elements of the evaluation.
- Laboratory evaluation is usually nonrevealing, and the cost/benefit ratio should be considered before extensive laboratory tests are performed

toid arthritis, viral hepatitis, thyroid disease, Sjögren's syndrome, myelo- or lymphoproliferative disorders, vasculitis, and mastocytosis.

Several historical points are particularly noteworthy. Idiopathic angioedema without urticaria does occur (<10% of all cases of idiopathic urticaria and angioedema). However, when confronted with angioedema without urticaria, the possibility increases for a diagnosis of hereditary angioedema, acquired angioedema associated with complement abnormalities and malignancy, and angioedema owing to angiotensin-converting enzyme inhibitor therapy. Angioedema that follows trauma and lasts longer than 48–72 h h suggests hereditary or acquired angioedema with complement abnormalities. Urticaria with individual lesions lasting longer than 24 h, particularly if there are cutaneous findings of purpura or ulceration, suggests a diagnosis of vasculitis. Urticaria coexistent with arthralgias, myalgias, and subjective fever suggests autoimmune disease, vasculitis, delayed pressure urticaria, myelo- or lymphoproliferative disorders, or infection associated with urticaria and angioedema. These infections include acute hepatitis, infectious mononucleosis, streptococcal disease, parasitic infestations, and systemic

fungal infections. Urticaria with fixed, pigmented skin lesions, with or without systemic symptoms of flushing or diarrhea, increases the likelihood of mastocytosis.

Physical Examination

The physical examination is limited to confirming lesions consistent with urticaria and angioedema, excluding a diagnosis of an associated disease, detecting papules consistent with arthropod assault, and identifying signs of vasculitis, such as purpura, petechiae, or ulcerative lesions. Specific forms of physical urticaria can be investigated with testing during the physical examination. The diagnosis of cold urticaria is confirmed by placing an ice cube in a plastic bag against the volar forearm for 4–5 min and observing for urticaria following removal (Fig. 4). Delayed pressure-induced urticaria is diagnosed by applying for 15–20 min a 15–20 lb weight on a selected area, such as the thigh or forearm. Urticaria and angioedema develop within 4–8 h. Elevation of core body temperature by exercising in a jogging suit or performing a stress test will trigger urticaria in subjects with cholinergic urticaria. Vibratory urticaria may be tested by having the subject hold a mixer or other vibrating equipment for 10–15 min. Dermatographia is tested by applying blunt trauma to the skin, or by scratching with an unexposed ballpoint pen or the wooden end of a cotton swab (Fig. 3).

Laboratory Assessment

Laboratory testing is almost never of value unless the history and physical examination suggest the possibility of a medical condition associated with urticaria and angioedema. An extensive, screening laboratory evaluation is not recommended and is not cost-effective. Tests that may be cost-effective include a complete blood count with differential, a chemistry profile with liver enzymes, urine analysis and possibly a thyrotropin-stimulating hormone level, total thyroid hormone quantitation, and erythrocyte sedimentation rate.

Additional laboratory tests should be considered in special circumstances. Thyroid autoantibodies have been reported in approx 15% of subjects with chronic urticaria and angioedema, and may be of clinical significance even if the subject is euthyroid with a normal examination of the gland. Cryoglobulins, VDRL, and cold agglutinins may be helpful in evaluating cold-induced urticaria. Complement studies, particularly CH50, C4, C1-esterase inhibitor, or C1q, may be useful if vasculitis or angioedema associated with complement abnormalities is suspected. An ANA or cryoglobulins could be helpful if vasculitis is suspected. C1q binding protein, an antibody that precipitates C1q in vitro, is detected in subjects with hypocomplementemic urticarial vasculitis. This test is performed in select laboratories with an interest in complement abnormalities but is available commercially. C1q binding protein should not be confused with C1q precipitation, an assay for immune complexes. Total C4 is generally low in hereditary angioedema between and during angioedema episodes, whereas C3 is normal except when angioedema occurs. C1-esterase inhibitor antigenic levels, the usual method of testing for C1-esterase inhibitor, are decreased in 85% of subjects with hereditary angioedema. Functional C1-esterase assays, which are more expensive and difficult than the antigen assays, are required to confirm a suspected diagnosis of hereditary angioedema in the other 15%. Acquired forms of angioedema associated with complement abnormalities are distinguished from hereditary angioedema by measurement of

C1q. C1q is decreased in the acquired varieties but is normal in hereditary angioedema. Intradermal injection of autologous sera is a clinical method for testing the presence of autoantibodies specific for the high-affinity IgE receptor or for IgE, although false positive and negative results occur. A positive response is the development of a wheal and flare response, which typically lasts up to 8 h. Laboratory testing usually not of value includes total IgE, cultures when no clinical evidence of infection is present, chest radiographs, immunoglobulin levels, lymphocyte subsets, and assays for parasitic infection, including stool for ova and parasites, unless features of infestation are noted.

TREATMENT

General Recommendations

The most effective treatment for urticaria and angioedema is to eliminate the trigger or cause of the condition. An elimination diet with subsequent challenge with the suspected food may be sufficient for food allergy or suspected food allergy. The rice and lamb diet is traditionally used if the affected subject has a suspicion or anxiety concerning food allergy without specific foods being suspected. There are no controlled trials to validate the use of a rice and lamb diet in this circumstance. Elemental diets, which eliminate all food allergens, could also be tried, but these are limited by cost and palatability. Restricted diets are recommended for 10 d to 3 wk to determine if the urticaria and angioedema resolve. Foods suspected are then introduced individually, approximately every 3–4 d. Another option is to perform epicutaneous skin tests with suspected food extracts and eliminate all foods with a positive wheal and flare response. The yield of this exercise in urticaria and angioedema is low, but occasionally a causal food will be identified. Confirmation of the causal role of the identified food requires blinded food challenge. Challenges may be single-blind initially and followed by a double-blind challenge if necessary. Challenges are best performed while the test subject is under close observation, since subsequent reactions may be more severe than the initial reaction. The approach to drug allergy is similar, although testing and challenges are even less likely necessary, since most drugs can be avoided if likely responsible for urticaria and angioedema. Physical urticaria and angioedema will improve with avoidance of the inciting physical factors, such as pressure, heat, vibration, rubbing of the skin, and UV light. Sun blocking agents and window glass are protective in some, but not all, forms of solar urticaria.

Antihistamine Therapy

H_1 Antihistamines

Histamine is a primary mediator of urticaria and angioedema, and therefore, antihistamine therapy is a mainstay of pharmacologic treatment. The pruritus of urticaria, the primary cause of patient discomfort, is significantly diminished by appropriate doses of H_1 antihistamines. The number, size, and duration of urticarial lesions are also mitigated by antihistamine therapy. However, the swelling of angioedema does not respond as well. Less sedating antihistamine therapy, for example, astemizole (Hismanal®) 10 mg/d, cetirizine (Zyrtec®, 10 mg/d), loratidine (Claritin®) 10 mg/d, and terfenadine (Seldane®) 60 mg twice a day, relieves itching but may not be as effective

Key Features of Therapy

- Antihistamines are the cornerstone of therapy; in some cases, the addition of an H_2 antagonist may be helpful.
- Tricyclic antidepressants, especially doxepin, may be the most effective antipruritic agent.
- Systemic corticosteroids are the most effective treatment but should be used judiciously only for incapacitating symptoms not responsive to maximal antihistamine treatment and usually should be reserved for acute, severe flares.
- Rarely, alternative agents, such as β-adrenergic drugs, hydroxychloroquine, nifedipine, colchicine, and dapsone may be of help.
- Emotional support and education are essential, since in many instances, the condition cannot be completely controlled.

as traditional, sedating antihistamines because of the lack of effect on associated anxiety. Cetirizine reduces the recruitment of eosinophils into cutaneous tissues, but this has not been proven to enhance the efficacy of this agent compared to the other H_1 antagonists.

There are six classes of variably sedating, first-generation antihistamines, all of which may be effective for treatment of urticaria and angioedema (Table 5). Some authorities recommend trials of individual agents from various classes to determine which is the most effective. Hydroxyzine is generally considered the drug of choice because of its efficacy, long tissue half-life, cost, and available syrup formulation to permit variation of dose. Long drug half-life is preferable, since blocking of the histamine receptor before the development of symptoms is more effective than waiting for symptoms before initiating therapy. Therapeutic half-life is the primary limitation of agents, such as diphenhydramine, in chronic therapy. Treatment with hydroxyzine is usually initiated at a dose of 5–10 mg three to four times a day and increased gradually, if tolerated, to 50 mg four times a day. Combination antihistamine therapy using two agents from separate classes may be tried if single drug treatment with maximum doses is not effective or not tolerated. There are limited data demonstrating the advantage of combination therapy, primarily with cyproheptadine and hydroxyzine. There are no data substantiating the frequently used strategy of combining terfenadine 60 mg administered in the morning with a sedating antihistamine, such as hydroxyzine, given in the evening. The rationale is to utilize the less sedating, more expensive agent during the day and the sedating, economical agent when sleep is anticipated. Although appealing, this plan has not been validated.

The major side effect of traditional antihistamine therapy is sedation. Individuals vary greatly in their perception of somnolence with treatment. Many subjects will not notice or complain of sedation, but studies demonstrate impairment without subjective awareness. Furthermore, long-term therapy does not necessarily eliminate the impairment. This has been shown for vigilance, judgment, and reaction time. Tests of coordination and driving skills also demonstrate impaired hand–eye coordination. Statistical studies have shown that individuals involved in fatal motor vehicle accidents are more likely to have taken a sedating antihistamine than subjects in motor vehicle accidents

Table 5
Chemical Classes of H1 Antihistamines and Representative Examples

Class	*Generic name*
Alkylamine	Chlorpheniramine
	Brompheniramine
Ethanolamine	Diphenhydramine
	Clemastine
Ethylenediamine	Tripelennamine
Phenothiazine	Methdilazine
Piperazine	Hydroxyzine
Piperidine	Cyproheptadine

without fatality. The alkylamine antihistamines, such as chlorpheniramine, are generally believed to result in a lower incidence of sedation than other first-generation antihistamines. Anticholinergic side effects are also common, and potentially serious, with first-generation antihistamine therapy. These include dry mouth, blurred vision, urinary retention, and tachycardia. Traditional antihistamines should be avoided in subjects with narrow-angle glaucoma or a predisposition to urinary retention, such as benign prostatic hypertrophy.

Second-generation antihistamines do not readily cross the blood–brain barrier because of their reduced lipid solubility. Thus, the occurrence of sedation with these agents is no greater than placebo. Anticholinergic side effects are likewise negligible. There is a concern over potential cardiac arrhythmia with astemizole and terfenadine therapy. Astemizole and terfenadine prolong the QT interval during cardiac repolarization. This effect is the result of interference with the slow potassium rectifier current, which is partially responsible for restoring membrane polarity after depolarization. If the levels of astemizole or terfenadine are increased or if a subject has a prolonged QT interval prior to therapy, there is a risk of developing a potentially life-threatening ventricular arrhythmia, Torsade de Pointes. Subjects at increased risk include those receiving other therapy that prolongs QT interval, individuals with hepatic disease, people with hypokalemia or hypomagnesemia, and subjects cotreated with agents that interfere with cytochrome p450 mixed-function oxidase system. Examples of drugs that interfere with cytochrome p450 are ketoconazole, itraconazole, and erythromycin, among others. Loratidine does not appear to have a similar effect on the QT interval and therefore is not a risk for ventricular arrhythmia. The question of whether first-generation antihistamines prolong the QT interval at high plasma levels has not been adequately studied.

H_2 Antihistamines

A 3–4 wk trial with H_2 antihistamine therapy may be beneficial in subjects with urticaria and angioedema who do not satisfactorily respond to H_1 antihistamine therapy at maximal recommended or tolerated dose. The rationale for this treatment is the presence in the cutaneous vasculature of H_2 receptors, comprising almost 10% of the total histamine receptors. H_2 antagonists, such as cimetidine or ranitidine, may be combined with maximal H_1 antihistamine, or alternatively, such agents as doxepin with both H_1

and H_2 antihistamine effects may be utilized (*see* Tricyclic Antidepressants). The clinical benefits of H_2 antihistamine therapy in urticaria and angioedema are generally limited.

Tricyclic Antidepressants

Tricyclic antidepressants have potent antihistamine properties. Doxepin, a heterocyclic variant of amitriptyline, has both H_1 and H_2 antihistamine effects. Doxepin is approx 800 times more potent on a molar basis than diphenhydramine and six times more potent than cimetidine. Clinical efficacy in the treatment of chronic idiopathic urticaria has been demonstrated with daily doses between 30 and 150 mg. Doxepin is the drug of choice if H_1 antihistamine therapy fails because of the long tissue half-life permitting twice a day administration, H_1 and H_2 antagonism with a single drug, availability of a concentrated syrup formulation facilitating dosing flexibility, and economic cost. The sedative and anticholinergic properties are the major side effects. No studies have been performed with the combination of doxepin with other antihistamines.

Corticosteroids

Systemic corticosteroid therapy is very effective in suppressing the signs and symptoms of urticaria and angioedema. This form of therapy should be used only in disease that has incapacitating symptoms despite maximal antihistamine therapy or in acute, severe flares of the condition. Corticosteroid side effects and the potentially prolonged duration of chronic urticaria and angioedema make this treatment ill-advised, except for the most severe of circumstances. The dose of corticosteroid is dictated by the severity of disease, but is usually initiated at approx 0.5–1 mg/kg/d. The corticosteroid is tapered over 7–14 days and discontinued. Following such treatment, other medical measures may become more effective. Occasionally, the corticosteroid cannot be discontinued, and alternate-day treatment, e.g., 10–25 mg every other day, is utilized until the urticaria and angioedema become less symptomatic. The alternate-day dosing significantly reduces side effects. Antihistamines and occasionally other therapies, such as hydroxychloroquine, dapsone, nonsteroidal anti-inflammatory drugs, and methotrexate (*see* Other Therapy), are utilized simultaneously. Select individuals with delayed pressure urticaria, urticarial vasculitis, or recalcitrant disease may remain corticosteroid dependent for many months or longer. These subjects require frequent reassessment, instruction in corticosteroid side effects, initiation of measures to minimize weight gain and osteoporosis, and repeated trials with other therapeutic agents in the hope of discontinuing corticosteroid therapy.

β-*Adrenergic Therapy*

Epinephrine by subcutaneous-administration, 0.001 cc/kg of 1:1000 dilution with a maximum dose of 0.3 cc, is effective for acute management of exacerbations of urticaria and angioedema, particularly when laryngeal edema complicates an attack. Although this treatment does provide some immediate symptom relief, it should be kept in mind that idiopathic urticaria and angioedema almost never lead to sufficient airway edema to obstruct the airway. This is not the case for angioedema associated with acute reactions to medication, food ingestion, or insect stings. The angioedema of hereditary angioedema, which can lead to airway obstruction, is relatively resistant to epinephrine

therapy. Oral adrenergic drugs, such as ephedrine and terbutaline, have been used in chronic idiopathic urticaria and angioedema with only marginal success.

Other Therapy

The persistent nature of idiopathic urticaria and angioedema has led to trials of various treatments, usually in a small number of subjects and frequently in an uncontrolled fashion. The lack of large, double-blind trials in a condition with significant variation in symptoms limits the applicability of these treatments to an individual subject. However, when symptoms are uncontrolled or require corticosteroid therapy, consideration should be given to some of these agents.

Hydroxychloroquine (Plaquanil®) has been reported to have beneficial effects in chronic, idiopathic urticaria. The dose is 200 mg twice a day in adult subjects. The mechanism of action is unknown, but the beneficial effects hydroxychloroquine has on systemic lupus erythematosus, an autoimmune disease, suggests that a similar effect may occur in idiopathic urticaria. This seems particularly relevant in light of the report of autoantibody against the IgE F_c receptor or the F_c region of IgE in a significant number of subjects with chronic urticaria. An attraction of this therapy is the minimal side effects. Mild nausea and occasional leukopenia are the principal concerns. Pigmented retinopathy, a potentially irreversible complication of hydroxychloroquine, almost never occurs if the dose is <6–7 mg/kg/d. Ophthalmology examinations every 6–12 mo are recommended by the *Physicians' Desk Reference.*

Nifedipine, a calcium channel blocker, may reduce the manifestations of chronic urticaria in select subjects. The mechanism of action is also unknown but may relate to effects of calcium channels on mediator release from mast cells. The dose reported in the case reports in the medical literature is 10 mg three times a day. This treatment is generally well tolerated, except for occasional mild postural hypotension and dependent edema. The dose may be increased if no side effects are encountered.

Thyroid autoantibodies have been detected in 10–20% of subjects with idiopathic, chronic urticaria and angioedema. Urticaria has been reported to improve with thyroid supplementation in the presence of thyroid autoantibody, even when the affected subject is euthyroid. This treatment deserves consideration, since it is relatively safe compared to other alternative therapies.

Nonsteroidal anti-inflammatory drug (NSAID) therapy may be associated with clinical improvement in some subjects with delayed pressure urticaria and angioedema and mastocytosis. The use of this treatment in idiopathic urticaria may be relatively safe, but this strategy is complicated by reports of NSAIDs exacerbating idiopathic urticaria and angioedema in 10–20% of cases. Severe, even life-threatening reactions may occur in highly sensitive individuals, particularly those with asthma, and in subjects with mastocytosis.

Dapsone, stanazolol, and methotrexate have been described to have a corticosteroid-sparing effect in a small number of subjects. Dapsone may be more effective if a predominance of neutrophils is detected on cutaneous biopsy. Dapsone is generally administered at a dose of 50–200 mg/d. This treatment will result in a variable anemia and methemoglobinemia. Life-threatening hemolytic anemia will occur if dapsone is given to glucose-6-phosphatase-deficient individuals. The potential mechanism of action of stanazolol in idiopathic urticaria and angioedema is unknown. This treatment has been

reported more in women. This is of interest, since hormonally induced urticaria, particularly associated with progesterone, has been described and stanazolol suppresses hormone production. Stanazolol or danazol is the treatment of choice for hereditary angioedema. This treatment increases the C1-esterase inhibitor levels by enhancing hepatic production of the enzyme. Low-dose, weekly methotrexate may have anti-inflammatory effects that could be beneficial in chronic, corticosteroid-dependent urticaria. There is a potential of serious complications with methotrexate therapy, including neutropenia, interstitial pneumonitis, hepatic fibrosis, and very rare reports of opportunistic infections. Obviously, the decision to try methotrexate therapy in this circumstance would require in-depth discussion with the patient and consultants.

SUMMARY

Urticaria and angioedema are common clinical problems that provoke great anxiety in the affected subject and frustration in the treating physician. Acute disease is generally not a major issue, but the lack of identifiable etiology and pathogenetic mechanisms in the majority of subjects with chronic urticaria frustrates a rational approach to management. Symptomatic treatment with antihistamines and reassurance are fortunately all that is required in most. In the more severe cases or those complicated by other medical conditions, there are numerous options, but most have not been well studied. Potential complications of these alternative therapies should be well understood by the treating physician and discussed with the patient. An evaluation of the risk: benefit ratio may be difficult. The advice of Francis Peabody seems most appropriate when facing a patient with chronic urticaria and angioedema: "The secret of good patient care is to care for the patient."

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13 Atopic Dermatitis

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CONTENTS

INTRODUCTION

Atopic dermatitis (AD) is a complex, multifactorial disorder that was first described in the medical literature over 100 years ago. Although clinicians and researchers agree that this disorder is caused by many factors, the role of allergic disease has remained at the forefront of clinical research. In the late 19th century, Besnier provided a detailed description of a chronic, pruritic dermatitis beginning in infancy and showing associations with asthma and rhinitis. The term "prurigo Besnier" was subsequently used to describe these patients. In 1902, Brocq coined the term "neurodermatitis" to refer to a chronic, pruritic skin condition seen in patients with apparent nervous disorders. Coca (1933) was the first to denote the familial occurrence of hay fever, asthma, and eczema, and introduced the term "atopy" to describe the inherited nature of human hypersensitivity disorders. In 1933, Wise and Sulzberger condensed the past terminology into the descriptive term we use today—"atopic dermatitis."

From: *Allergic Diseases: Diagnosis and Treatment*
Edited by P. Lieberman and J. Anderson Humana Press Inc., Totowa, NJ

Key Clinical Features of Atopic Dermatitis

- A chronic, eczematoid dermatitis with 90% of cases beginning before age 5;
- Characteristic distribution pattern that varies with age;
- Intensely pruritic;
- Fifty to 80% of patients also suffer from allergic respiratory disease.

NATURAL HISTORY

Prevalence

Although AD is known to be a common skin disorder, the true prevalence is unknown and has been the subject of much debate among physicians and clinical investigators in many fields of medicine. The prevalence in pediatric populations has been estimated to range from 1.1 to 4.3%; however, comprehensive, longitudinal surveys have not been performed to date. In addition, most investigators agree that the prevalence of this condition is affected by many factors, such as geographic location and climate, thereby making prevalence studies difficult. It is well recognized that AD is more prevalent in industrialized countries compared to nonindustrialized countries or tropical regions.

Disease Course

AD is a chronic disease of infants, children, and young adults. Onset of disease is typically during early infancy. Sixty percent of affected individuals manifest characteristic lesions during the first year of life. Ninety percent of individuals will be affected by age 5 yr. The remaining individuals will typically manifest disease during late childhood or adolescence. It is rare for symptoms to begin during adulthood and should be a clue to question the accuracy of diagnosis.

The clinical course is variable and unpredictable. Some infants and children will have a mild course with spontaneous remission by 2–3 yr of age. Others will have more persistent disease with a chronic unremitting course throughout childhood and even into adulthood. Still others will have a waxing and waning course highlighted by unexplained remissions of varying degrees followed by equally unexplained exacerbations.

Characteristic Distribution

AD is typically divided into three clinical phases based on age of onset. The infantile phase is from birth to 2 yr of age. The onset in this group is typically after 2 mo of age, but onset during the first few weeks of life may be seen. The childhood phase is between 2 and 11 yr. The adolescent and adult phase begins at age 12 yr and proceeds through adulthood. Each of these phases has a typical distribution of skin lesions that can prove useful in diagnosis (Fig. 1).

The infantile phase is characterized by erythematous, pruritic, exudative, maculopapular lesions that contrast to the more dry, lichenified lesions seen later in childhood and adult life. In infancy, these lesions first appear on the cheeks, forehead, and scalp. Progression then occurs to involve the trunk and extensor surfaces of the extrem-

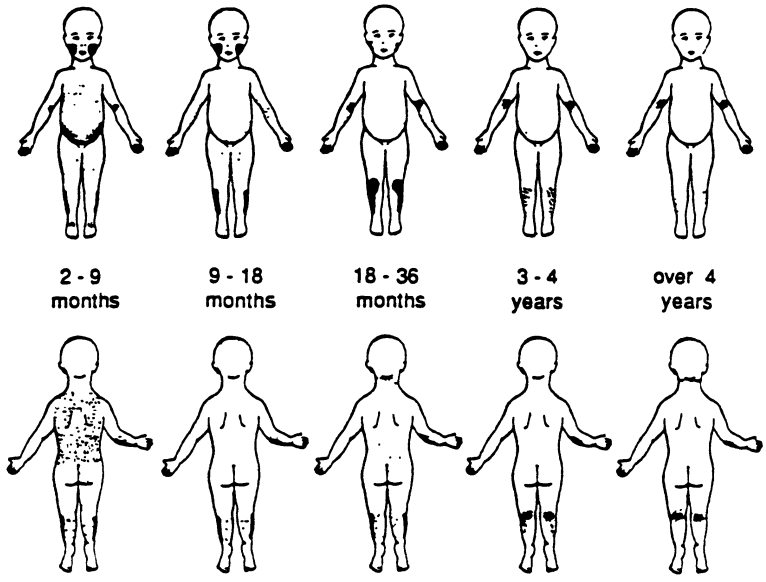

Fig. 1. Distribution of AD in relation to age (adapted from Sedlis, *J Pediatr* 1965; 66 (2): 235).

ities. As the infant grows older, the distribution of lesions may change to involve the entire extremity surface or the more typical flexural distribution of childhood.

During the childhood phase, lesions of AD are typically dry and involve a more flexural distribution of the extremities. The face, with the exception of the lips and perioral region, is less commonly affected by the age of 4–5 yr. The hands can be especially difficult areas to control in this age group. Intense pruritus and secondary scratching can produce a very anxious, hyperactive child.

The adolescent and adult phase is most commonly manifested as lichenified, pruritic macular lesions involving the face, neck, upper trunk, and flexural regions of the extremities. Many young women in their 20s experience hand involvement (i.e., hand eczema) as the first or only manifestation of AD. As previously noted, the onset of disease later in life is very uncommon, and should be a clue to search for other etiologic factors or diseases.

PATHOGENESIS

Role of Allergens

There is a strong correlation of AD with other atopic conditions, such as asthma and allergic rhinitis. As many as 50–80% of children with AD will develop allergic respiratory disease later in life. In addition, many clinicians note the peculiar tendency of AD and asthma to alternate in their courses in some patients. This observation is unexplained and inconsistent with episodes of both diseases occurring simultaneously on occasion. Owing to earlier historical observations of AD associated with other atopic diseases, investigators have explored the role of various allergens as causal factors in these diseases (Table 1).

Key Features of the Pathogenesis of Atopic Dermatitis

- Immediate hypersensitivity may be key to pathogenesis in the majority of patients
  - Lesions can be reproduced by patch testing to aeroallergens;
  - Exacerbations clearly related to ingestion of foods to which patient is allergic; and
  - Many patients have IgE-mediated allergic responses to microorganisms growing on the skin
- Nonimmunologic factors, such as climate and nonspecific irritants, may play a role

Table 1
Common Allergens in AD

Aeroallergens
Pollens
Molds
Dust mite
Animal dander
Cockroach
Food allergens
Milk
Egg
Soy
Peanuts
Wheat
Shellfish
Fish
Microorganisms
Bacteria
S. aureus
Streptococci
Fungi/yeasts
P. ovale/orbiculare
Trichophytan species

Aeroallergens

Pollens were the first aeroallergens reported in association with AD. Ragweed pollinosis has been of particular interest with clinicians citing case reports of patients with seasonal exacerbation of AD and clearing in a pollen-free environment. In the 1950s Tuft performed intranasal challenges with ragweed pollen and noted rhinorrhea and itching of affected skin areas in AD patients. More recently, investigators have shown positive prick skin tests and patch tests to common pollens in patients with seasonal distribution of their AD. In a recent study of children, Wananukul found 90% of AD children tested with epicutaneous patch testing to develop eczematous lesions in one or more AD predilection sites when tested with dust mite, cockroach, mold, and grass mix.

Others have shown positive immediate skin tests to birch pollen in AD patients who had worsening of their disease during the birch pollen season.

Mold allergens have also been implicated as causal factors in patients with AD. Tuft induced symptoms of dermatitis in his patients following inhalation challenge with *Alternaria* when compared with talc powder or pine pollen. Rajka has also demonstrated eczematous lesions in two of five atopic individuals with AD following inhalation of mold extract.

The largest body of scientific and clinical data regarding aeroallergens and atopic diseases exists in reference to dust mite allergy. Sensitivity to the dust mite was first examined in patients with asthma. Reports soon followed of improvement in AD when patients were placed in a dust-free environment and subsequent aggravation of symptoms after exposure to dust. Platts-Mills and colleagues have performed extensive studies of dust mite antigen and atopic disease association. They and others have shown positive prick skin testing and patch testing to dust mite antigen in patients with AD. In a recent epidemiologic survey, the homes of patients with moderate to severe AD showed a higher dust mite concentration than controls. Elevated serum levels of dust mite-specific antibody and increased basophil sensitivity have also been shown in AD patients when compared with controls. Several groups of investigators have also demonstrated an increased lymphocyte response and specific cytokine profile production in patients with AD and evidence of dust mite allergy. Perhaps the best clinical evidence for dust mite allergen playing a role in the AD condition of some patients comes from reports of patients showing improvement when living in a dust-free environment and having flares of disease on return to an environment of exposure to dust mite.

Two other types of aeroallergens are felt to play a role in the pathogenesis of AD—animal dander and cockroach allergens. Both of these allergen groups have been studied in association with asthma and allergic rhinitis, and are believed to be important factors in certain susceptible individuals. Less scientific information is available with regard to AD; however, anecdotal clinical experience would support their causative roles. Of the animal danders, cat and dog dander are implicated most commonly in atopic disease states. Cat dander allergy, in particular, can manifest as severe in some atopic individuals, especially those with asthma. Cockroach allergens have been recognized more recently in atopic disease, especially in endemic areas and climates. In Wananukul's recent study of atopic children, many of them had positive prick and intradermal skin tests to animal dander and cockroach, indicating the possible relevance of these allergens in atopic disease. More study is needed to define further the role of animal dander and cockroach allergens in AD.

Foods

Adverse reactions to foods have been reported in the medical literature since the early 1900s when Smith reported the case of a man with "buckwheat poisoning." In 1918 Talbot was one of the first physicians to observe an improvement in a patient's eczema while on a milk and egg restriction diet. Tuft (1950s) considered food allergy to be the most important pathogenic factor in infants and young children with AD, yielding to inhalant allergies in older children and adults. Since that time, many investigators have studied children with AD and food hypersensitivity. In general, they have shown

that dietary manipulation has resulted in dramatic improvement in many patients with AD, especially young children.

Bock and colleagues were the first to establish the use of double-blind, placebo-controlled food challenges (DBPCFC) to assess patients with suspected food hypersensitivity. Because there is poor correlation between allergen-specific IgE antibodies (skin tests or radioallergosorbent test [RAST]) and clinical symptoms related to food hypersensitivity, oral food challenges (both open and blinded) have been crucial in assisting many investigative groups in the study of food hypersensitivity and AD. Sampson first reported findings of food hypersensitivity in 26 children with AD. These findings were confirmed during a study in our institution in which 46 children with AD were studied with DBPCFC. Positive challenges were detected in 33% of patients with 91% reacting to only one or two foods. These groups have shown a direct correlation between hypersensitivity to foods (Table 1) and the development of AD. In addition, these groups have consistently reported improvement in AD in food protein-sensitive patients while on food elimination diets.

Perhaps the largest body of information regarding AD and food hypersensitivity has been provided by Sampson and coworkers. To date they have evaluated 400 children with AD for food hypersensitivity by performing 1303 initial DBPCFC to suspected foods. Egg, milk, peanut, soy, and wheat accounted for 87% of positive food challenges with egg sensitivity being the most prevalent. Cutaneous symptoms were seen in 75% of positive challenges. The most common cutaneous manifestation consisted of a pruritic, erythematous morbilliform rash involving the AD predilection sites. Other symptoms noted during positive challenge included respiratory (stridor, wheezing, nasal congestion, rhinorrhea, and sneezing) and gastrointestinal (nausea, vomiting, abdominal cramping and/or diarrhea) symptoms. All patients found to be allergic to particular foods were placed on an appropriate avoidance diet of that food. Virtually all patients reported improvement in symptoms, either noted as complete resolution or marked clearing.

Sampson and colleagues have presented studies of mediator release that provide further evidence that food-specific IgE-mediated mechanisms play a role in the pathogenesis of AD. They have demonstrated increased plasma histamine levels in AD patients following a positive food challenge, increased spontaneous histamine release from basophils in patients with AD and food hypersensitivity, spontaneous release of a cytokine (histamine-releasing factor [HRF]) from mononuclear cells in these patients, and increased cutaneous hyperirritability to a variety of minor stimuli. These mediators and the associated cutaneous hyperirritability were all noted to be diminished to normal levels after 6–9 mo of food allergen avoidance.

In an earlier study examining the natural history of patients with AD and food hypersensitivity, Sampson reported that 26% of patients lost their clinical hypersensitivity during the first year of allergen avoidance and 11% lost reactivity during the second year. Therefore, Sampson and others have shown that most children tend to "outgrow" their food hypersensitivity to most foods early in life. Some of these children also show subsequent resolution of their AD, whereas others manifest aeroallergen sensitivity that seems to perpetuate the AD cycle.

Through the years, much attention has focused on the role of maternal dietary restriction during pregnancy and lactation in the prevention of AD and food hypersensitivity.

The most current and comprehensive information to date comes from Zeiger and colleagues. This group has prospectively followed 288 American children from birth through age 4 yr and 125 of these children through age 7 yr. Some mothers and infants were randomized to a prophylactic group consisting of maternal avoidance of cow milk, eggs, and peanuts during the third trimester of pregnancy and during lactation; use of a casein hydrolysate formula for supplementation or weaning; avoidance of all solid foods for 6 mo; and avoidance of defined allergenic foods for up to 24 mo. Others provided a control or "untreated" group in which no prophylaxis was implemented. After 7 yr, the only atopic parameters affected between groups were the prevalence of food allergy and milk sensitization prior to age 2. No difference was seen in the prevalence of AD, asthma, allergic rhinitis, food sensitization, or positive skin tests to inhalant allergens. Other studies in children have shown a direct correlation between the number of solid foods introduced before age 6 mo and the prevalence of AD at age 2 yr. These and other studies indicate the potential role of food allergens in the development of AD and the potential benefits of early allergen avoidance in some high-risk infants.

Microorganisms

The role of microorganisms in the pathogenesis of AD has received much attention in recent years. Their potential role as complicating skin pathogens has long been recognized as important, but more recently their role as "allergens" perpetuating the allergic response has been of particular interest. It is postulated that the altered skin barrier seen in patients with AD provides a portal of entry for various pathogens to gain access to the immune system, thus activating mast cells, basophils, Langerhans cells, and other immune cells (Fig. 2). The primary classes of microorganisms involved include bacteria and yeasts.

The most extensively studied and widely recognized microorganism of importance in the disease process of AD is *Staphylococcus aureus*. *S. aureus* skin colonization of both affected and normal skin has been shown to be increased in patients with AD compared to controls. Some investigators have demonstrated colonization in over 90% of lesions in some individuals with AD. In addition, elevated IgE-specific antistaphylococcal antibodies have been demonstrated in sera of patients with AD. More recently, investigators have focused on the role of staphylococcal exotoxins in the disease cycle of AD. These studies have focused on the role of stimulating T-cell-dependent IgE production and subsequent enhancement of the allergic response. Evidence for an IgE-mediated mechanism has been supported by Neuber's reports of increased CD23 (low-affinity receptor for IgE) expression in cells from AD individuals following stimulation with *S. aureus*. Leung and coworkers have reported specific IgE antibodies to staphylococcal exotoxins produced from staphylococcal organisms grown from the skin of 32 of 56 AD patients. Basophils from 10 AD patients with IgE antibodies to these exotoxins released histamine in response to specific staphylococcal exotoxins. Basophils from normal individuals or from patients with AD, but without IgE, antiexotoxin antibodies failed to release histamine after exotoxin stimulation. Hofer has also presented data that low concentrations of toxic shock syndrome toxin-1 (TSST-1) are able to stimulate mononuclear cells from AD patients to produce IgE in a T-cell-dependent fashion. These groups and others have also suggested that these exotoxins may function as "superantigens," thereby perpetuating the immune response by stimulating T-cell prolifera-

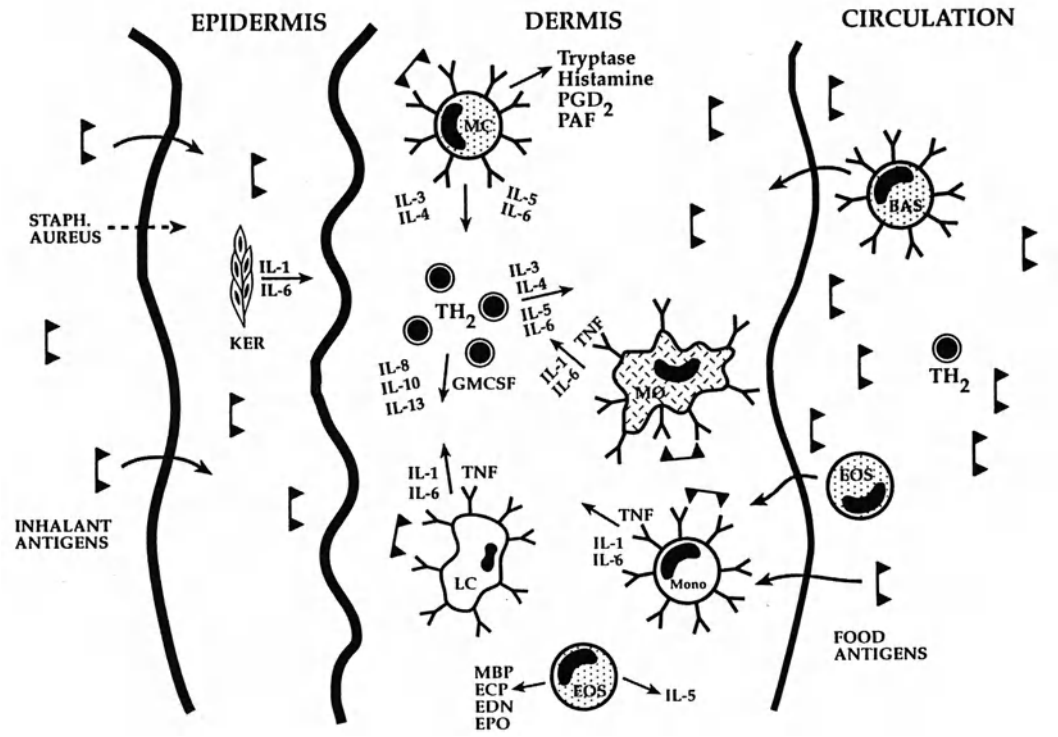

Fig. 2. Schematic representation of the immunopathological events in AD. Allergens transported via circulation or through fissures in the skin enter the epidermis and dermis, and activate local inflammatory cells. These cells secrete a variety of mediators and cytokines that perpetuate the cutaneous inflammatory response. TH_2 = T-lymphocytes capable of secreting IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, GM-CSF. Ker = keratinocytes, MC = mast cells, LC = Langerhans cells, Eos = eosinophils, Mono = monocytes, Bas = basophils, Mϕ = macrophages (adapted from Sampson HA. *Acta Derm Venereol* 1992; 176: 34–37).

tion independent of the usual allergic mechanisms. To emphasize further the role of *S. aureus* in the AD process, it has been clearly demonstrated that patients with AD show a better clinical response when treated with combinations of antistaphylococcal antibiotics and topical steroids than with steroids alone. Other bacteria, such as *Streptococcus* species, may also be important, but little clinical or investigative information exists to document their role.

Various species of yeast organisms have been implicated as causal factors in the pathogenesis of AD. *Pityrosporum ovale* and its gestational counterpart, *Pityrosporum orbiculare* are lipophilic yeasts that may inhabit the skin of all individuals with predilection for the neck, face, and upper trunk. Colonization is more commonly seen in older children and adults than in infants and younger children. Many investigators have shown a strong correlation between active AD lesions and specific antibodies to *P. ovale*. The antibodies have been demonstrated via prick skin testing and serum analysis via radioallergosorbent tests (RAST). Wessels showed the presence of *P. ovale*-specific IgE antibodies in 49% of AD patients. In addition, patients with head, neck and upper

trunk distribution of AD lesions and evidence of specific antibodies to *P. ovale* have been reported to show clinical improvement following ketoconazole therapy. Although not conclusive, these data suggest the pathogenic role of *Pityrosporum* species in some patients with AD and emphasize the need for consideration when refractory AD in the typical head and neck distribution is seen, especially in older children and adults. The possible role of other yeasts, such as *Candida albicans* and *Trichophyton*, has been implicated in the pathogenesis of AD; however, more extensive study is needed to draw firm conclusions.

Role of Environmental Factors

AD is a complex, multifactorial disease. The course of the disease is influenced by many primary and secondary factors that are often difficult to tease apart. Environmental factors frequently act as "triggers," causing exacerbations of disease, yet they are not primary causes of the underlying disease.

Climate

Several environmental factors can influence the course of disease in AD. One of the most important, yet often obscure, factors is climate. Individuals will respond differently to various climatic influences. Most authors report disease intensification during the winter months with reports of patients having the most comfort during the months of summer. Rajka has reported that improvement during the summer may be owing to better sebum and sweat secretion, UV rays from sun exposure, exposure to water during swim activities, reduced exposure to indoor allergens (i.e., dust mite and molds), less exposure to infection, and less psychosocial stressors during summer vacations. He also mentions that some of these same influences may in fact aggravate the skin condition of others patients. Sulzberger, Tuft, and others have noted the impaired sweating mechanism in patients with AD, making excess sweating and strong heat adverse factors in those individuals. UV light exposure without appropriate skin protection can also be harmful. Although indoor allergen exposure may be minimized during summer months, outdoor allergen exposure (i.e., grass pollens) may be exacerbating in some regions. As a general rule, cold dry weather is more aggravating to patients with AD secondary to the drying effect. Hot humid weather may also be aggravating because of increased perspiration and the increased potential for secondary skin infection. Extremes or sudden changes of any climatic condition (i.e., temperature and humidity) can be aggravating to patients with AD, most likely secondary to an impaired ability for immediate skin adaptation. Several reports have emphasized the beneficial effect of sunny climates, such as California or Florida, or dry, warm climates as found in Arizona. As previously stated, these factors are only secondary in the large majority of patients and vary individually.

Irritants

Factors other than primary irritants (i.e., allergens and infection) may complicate the course of AD. Clothing fabrics can influence the comfort level and the amount of pruritus experienced by AD patients. Wool fabrics clearly provide the most irritation and should be avoided in patients with AD. Synthetic fibers, such as nylon and polyester, may also be poorly tolerated by some individuals. Cotton is generally the fabric that provides the most comfort and least pruritic potential, and its use should be emphasized to patients.

Certain laundry detergents, bleaches, soaps, and household cleaning chemicals act as irritants for patients with AD. Mild laundry detergents without bleach are generally better tolerated. Washing clothing through a rinse cycle twice usually ensures removal of the detergent and may be beneficial in some sensitive patients. Mild skin soaps should also be used in AD patients for bathing. They are generally less drying, less irritating, and less likely to induce pruritus. Skin should be protected from household cleaners by wearing protective gloves or clothing. The skin barrier is frequently altered in AD and will not withstand the general intrusions that normal skin can endure.

Some foods can also act as triggers of irritation and pruritus. Certain fruits and vegetables, such as tomatoes and citrus fruits, are especially irritating in some individuals. These foods are not primary allergens, but rather irritants causing pruritus secondary to their acidic composition.

Psychosocial Factors

Most clinicians agree that psychosocial factors influence the disease process of AD and further agree that these factors remain secondary and not primary in disease etiology. Emotional upset, stress, job or school tension, and unstable or unsupportive home environments all can contribute as exacerbating factors. Some investigators have stated that these psychological influences may lead to autonomic dysregulation, abnormal vascular responses, and mediator release that all act to trigger an adverse response. In addition, the chronic pruritus seen in all patients with AD, especially those with severe disease, will cause sleep disturbance, hyperirritability, and emotional distress, which contribute to the viscous cycle. Although not primary causes of disease, these issues must be addressed in caring for patients with AD to provide maximal symptomatic relief during periods ofdisease exacerbation. These issues are especially important in children and adolescents and may occasionally require psychological as well as medical, intervention.

Occupation

Choice of career or occupation may strongly influence the disease state for some adult patients with AD. Surveys have reported more frequent AD in occupations in which exposure to dust, wool, textiles, or chemicals is common. The dry, hyperirritable skin of AD is prone to cracking, scaling, and infection following exposure to irritants. For this reason, patients in a workplace of high exposure have frequent or persistent flares of disease. Studies have reported that 65–75% of AD patients report hand eczema, many related to nonspecific irritants in the workplace. The consequences of hand dermatitis and exacerbation of AD may be quite serious in some individuals, requiring a change of duties or occupation to minimize exposure to irritants.

GENETIC ASSOCIATIONS

Like other atopic conditions, AD has a strong genetic predisposition. As many as 60–80% of patients with AD have a family history of a first-degree relative with AD, asthma, or allergic rhinitis. In studies of twins, Rajka reported a much higher concordance for atopy in monozygotic twins, whereas AD alone revealed only a 50% concordance in both monozygotic and dizygotic twins. Rajka's data cast doubt on the strictly hereditary influence, yet underscore the importance of the combination of hereditary

Key Features of Diagnosis

- There is no single diagnostic marker, and therefore, the diagnosis is dependent on a global evaluation;
- Morphology, distribution, pruritus, and associated atopic respiratory diseases are noteworthy features of history and physical examination; and
- Laboratory findings of peripheral eosinophilia, elevated serum IgE, and positive allergy skin tests can be markers of the disease.

and environmental factors in the disease process. Numerous reports have suggested HLA associations among families with atopic disease in general and AD specifically. These data are not definitive at present and suggest that a single set of genes is not responsible for atopic disease inheritance. Multiple patterns of disease inheritance, such as autosomal dominance, autosomal recessive, and multifactorial inheritance, have been found emphasizing the obvious complexity of genetic influence on the disease process. Throughout all these studies, however, it is maintained that individuals from atopic families are at greater risk for development of atopic disease in some form.

CLINICAL MANIFESTATIONS

History

AD typically begins early in life, most commonly with skin lesions developing in the first 6 mo. Although this pattern is typical, alterations in presentation frequently occur. A careful history can therefore be useful in making the diagnosis of AD. As noted previously, a family history of atopic disease may provide a clue to the etiology of a patient's skin disease. As many as 80% of patients with AD have a positive family history of atopy. A comprehensive history with regard to possible exacerbating triggers can also be helpful. These triggers may include foods, seasonal allergens, environmental conditions, irritants, emotional distress, and occupational exposures. A careful history will often uncover an exacerbating factor that is unapparent to the patient or the physician. The most prominent and persistent feature detected by historical evaluation is intense pruritus associated with a chronically relapsing course of skin disease.

Physical Findings

Although typical distribution of lesions can be detected during various stages of development (Fig. 1), no firm diagnostic pattern is seen among all patients. The diagnosis of AD therefore relies on information compiled from all aspects of the clinical history, physical examination, and laboratory data. Hanafin and Rajka have provided useful guidelines to assist in diagnosing AD (Table 2).

The rash of AD typically begins as an erythematous, papulovescicular eruption that progresses to a scaly, lichenified maculopapular dermatitis with time. Weeping, crusting lesions of the head, neck, and extensor surfaces of the extremities are common in infancy (Fig. 1). These lesions may involve the entire body surface, yet the diaper area may be spared. The scalp is often affected in infants with some having features of a concomitant scalp seborrhea. Because of intense pruritus and scratching, traumatic injury

Table 2
Guidelines for the Diagnosis of AD[a]

Must have three or more basic features:
Pruritus
Typical morphology and distribution
Flexural lichenification or linearity in adults
Facial and extensor involvement in infants and children
Chronic or chronically relapsing dermatitis
Personal or family history of atopy (Asthma, allergic rhinitis, AD)
Plus three or more minor features:
Xerosis
Ichthyosis/palmar hyperlinearity/keratosis pilaris
Immediate (Type I) skin test reactivity
Elevated serum IgE
Early age of onset
Tendency toward cutaneous infections (especially *S. aureus* and herpes simplex)/impaired cell-mediated immunity
Tendency toward nonspecific hand or foot dermatitis
Nipple eczema
Cheilitis
Recurrent conjunctivitis
Dennie-Morgan infraorbital fold
Keratoconus
Anterior subcapsular cataracts
Orbital darkening
Facial pallor/facial erythema
Pityriasis alba
Anterior neck folds
Itch when sweating
Intolerance to wool and lipid solvents
Perifollicular accentuation
Food intolerance
Course influenced by environmental/emotional factors
White dermographism/delayed blanch

[a]Hanafin, Rajka. *Acta Derm Venereol* 1980; suppl. 92: 44.

occurs over time providing a portal of entry for secondary bacterial infection. The early, erythematous lesions will frequently discolor over time and become dry, hyperpigmented lesions as seen in chronic dermatitis of the older child. Older children and adults have a more flexural distribution of lesions (Fig. 1). Lesions are typically dry, lichenfied maculopapular lesions. These lesions commonly remain intensely pruritic with resultant scratching, traumatic skin injury, and secondary infection. Hyperpigmentation of chronic lesions is seen with areas of hypopigmentation from older, healed AD lesions. Dry skin, ichthyosis, hand eczema, and chronic chelitis may also be prominent features of the disease. Skin lichenification may be persistent long after "active" dermatitis lesions resolve.

Clinicians have long recognized that patients with AD have a generalized "pallor" to their skin. This has been attributed to an abnormal vascular response that can be demon-

strated by the abnormal "blanching" response seen in these patients. This delayed blanching response can be seen in both affected and normal skin of AD patients as demonstrated by application of pressure or cold on the skin. In addition, these patients will frequently demonstrate "white dermographism." When the skin of an AD patient is stroked with a blunt object, a red line will form and then will be rapidly replaced by a white line without an associated wheal. Under the same conditions, normal skin will develop a red line owing to capillary dilatation, an erythematous flare caused by arteriolar dilatation, followed by a wheal secondary to the leaky, dilated capillaries. These abnormal vascular responses of AD have also been implicated in the temperature instability and poor regulatory responses seen in some patients.

Another prominent physical finding in patients with AD is an impaired sweating mechanism. Several investigators have documented this phenomenon with patients demonstrating less sweating under periods of stimulation. In addition, patients frequently complain of increased pruritus during periods of sweating. An increased transepidermal water loss has also been noted in patients with AD. This has been attributed to fewer sebaceous glands and less total lipid content of AD skin. All of these findings contribute to the clinical manifestations of dry skin and increased pruritus.

LABORATORY FINDINGS

Laboratory tests provide few clues to the diagnosis of AD. Several parameters can be helpful in eliciting triggering agents and underlying causes of disease, but none are diagnostic.

Hematologic Findings

Peripheral blood eosinophilia is commonly seen in patients with AD. Eosinophils usually comprise 5–10% of the total white blood cell count in AD patients. The degree of eosinophilia typically does not correlate with the degree of disease severity and is generally not a useful parameter to follow disease activity. Eosinophil mediators, such as major basic protein and eosinophil cationic protein, have been found in the circulation and biopsy specimens of patients with AD. Eosinophil cationic protein has been found in increased amounts in the circulation of AD patients with disease activation compared to AD patients with inactive disease or normal controls. This parameter has therefore been proposed as a useful marker for disease activity. More information is needed to determine if this parameter is actually a valid means of following the disease status in AD.

Serum IgE Antibody

Many investigators have found a correlation between elevated serum IgE concentrations and the presence of AD. Juhlin reported that 82% of AD patients evaluated had elevated serum IgE levels. In two subsequent surveys, Johnson and O'Loughlin reported the incidence of elevated IgE in AD to be 43 and 76%, respectively. Both noted that increased levels were seen more commonly in patients suffering from more severe disease and in those with concomitant atopic respiratory disease. In addition, these investigators reported a significant number of patients with typical AD and normal IgE concentrations. Other groups have also found elevated IgE levels in nonatopic individuals. At present, most investigators agree that the finding of an elevated serum IgE con-

centration is a secondary, not a primary, phenomenon. Serum IgE determinations in patients with AD provide little practical benefit in the diagnosis or management of patients with AD.

Skin Test Reactions

Prick and intradermal skin tests to various aeroallergens and food allergens are commonly used in the assessment of AD, and provide the most sensitive test for allergen detection. Controversy exists among allergists and dermatologists with regard to the clinical relevance of positive tests. Some investigators have reported that as many as 80% of individuals with AD will have positive specific IgE to a variety of allergens. This finding has been explained by some groups to be nonspecific and only an indicator of a generalized atopic state. Others report the clinical significance of specific IgE antibody and skin test reactivity in some patients with AD and report the observation of clinical improvement while instituting specific allergen avoidance. Knowledge of the allergens eliciting positive skin test reactions can be used as a clinical guide for the management of disease and detection of exacerbating conditions. These tests must be interpreted with caution. The presence of a positive skin test to an aeroallergen or a food allergen may not have strict clinical relevance and must be analyzed in light of the clinical history. For aeroallergen sensitivity, findings of seasonal distribution of other associated disease, such as allergic rhinitis and asthma, may provide additional clues for interpreting positive skin tests and instituting appropriate avoidance procedures. In the case of food allergen sensitivity, Sampson found prick skin tests to have an excellent negative predictive accuracy of 82–100% but a poor, highly variable, positive predictive accuracy of 25–75% when compared to blinded food challenge. Positive results must be correlated with the clinical history and dietary assessment, and then confirmed with a trial of an allergen elimination diet and subsequent food challenge.

RAST

RAST provide another, less sensitive method of evaluating a patient for the presence of IgE antibody to specific allergens in the serum. RAST can be performed on patients with AD in whom the extent of body surface involvement and severity of the dermatitis prohibits skin testing. These tests are less reliable than skin testing, especially when assessing for food allergen sensitivity. Like prick skin tests, Sampson found that RAST had an excellent negative predictive accuracy approaching 100%, but a poor positive predictive accuracy of 0–57% when compared to blinded food challenge. These findings limit their usefulness, but may still provide clinical clues, especially when negative results are found.

HISTOPATHOLOGY

The appearance of AD lesions on routine histologic specimen is not pathognomonic and can frequently be seen in a variety of inflammatory skin disorders, such as contact dermatitis, acute photoallergic dermatitis, and inflammatory pityriasis rosea. The histopathologic changes detected depend on the stage of the lesion (Fig. 3). These stages are typically divided into acute and chronic.

The acute AD lesion (Fig. 3B) is characterized by hyperkeratosis, parakeratosis, and hyperplasia of the epidermis, with an absence or diminution of the granular cell layer. In

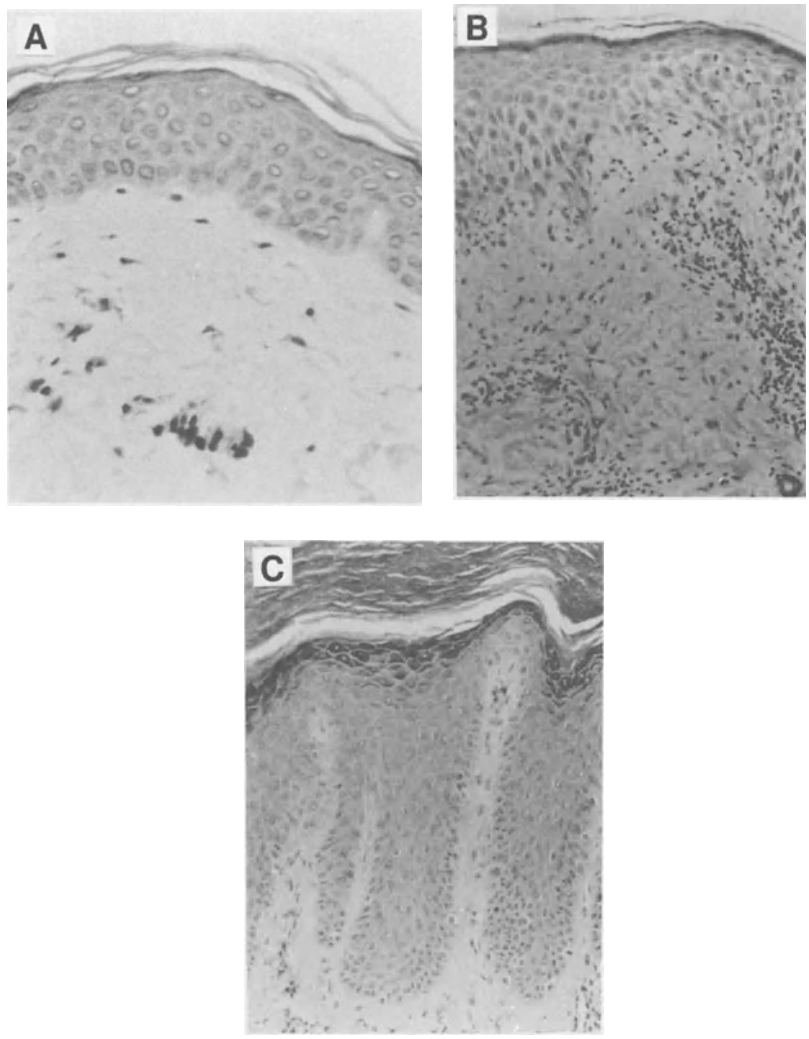

Fig. 3. Skin biopsy specimens of normal skin (**A**), acute lesions of AD (**B**), and chronic lesions of AD (**C**).

addition, spongiosis secondary to intercellular and intracellular edema of keratinocytes, is prominent. A marked mononuclear cell infiltrate, composed primarily of lymphocytes and occasional monocytes, is seen around the dermal venous plexes. Normal numbers of mast cells, basophils, eosinophils, and Langerhans cells are found in the acute lesions.

Chronic lesions of AD (Fig. 3C) are characterized by marked hyperkeratosis of the epidermis with elongation of the rete ridges, prominent parakeratosis, and papillomatosis of the dermis. Only minimal amounts of spongiosis are detected. There is a marked inflammatory infiltrate in both the perivenular and intervascular areas that consists of monocytes, macrophages, and lymphocytes. Increased numbers of mast cells and

Langerhans cells can also be detected, but eosinophils are rarely found. Demyelination and fibrosis of the cutaneous nerves can be seen at all levels of the dermis.

Immunohistochemical staining using monoclonal antibodies (MAb) in specimens from acute and chronic skin lesions reveals that the predominant lymphocytic infiltrate consists of T-cells bearing the CD3, CD4 surface antigens (i.e., helper/inducer T-cell phenotype), and only occasional CD8-positive surface antigens (i.e., cytotoxic/suppressor T-cell phenotype). There are no natural killer cells or B-cells in the lymphocytic infiltrate. In addition, most cells express MHC Class II surface antigens, indicating an "activated" state. Increased numbers of Langerhans cells (i.e., CD1a and HLA-DR antigen-positive cells) are detected in lesional biopsies, especially in chronic lesions. These Langerhans cells and associated infiltrating macrophages display IgE molecules bound to their surface. Epidermal keratinocytes located in the dermis of lesional skin also show evidence of activation with increased surface expression of MHC Class II antigens and expression of the adhesion molecule, intracellular adhesion molecule-1 (ICAM-1). These cells are believed to be of importance with regard to antigen presentation and processing, and subsequent lymphocyte activation and trafficking.

Although biopsy specimens from lesional skin of AD show few eosinophils, Leiferman and others have demonstrated large amounts of major basic protein (MBP) deposition in the chronic skin lesions. MBP is a cationic protein released by activated eosinophils and has been found to have cytolytic activity in lesional skin of patients with AD, as well as in respiratory biopsies from asthmatics. In addition, MBP has been shown to be capable of stimulating mast cell and basophil degranulation. Other investigators have found increases of other eosinophil mediators (i.e., eosinophil cationic protein and eosinophil-derived neurotoxin) in the biopsy specimens and skin blister fluid of patients with AD following allergen challenge. These findings support the important role of eosinophils and their mediators in the pathogenesis of AD.

IMMUNOPATHOLOGY

Although the full understanding of the immunopathology of AD remains to be elucidated, various immune abnormalities can be routinely detected in these patients. Findings include elevated serum IgE, abnormal delayed-type skin reactivity to common antigens (i.e., tetanus antigen), decreased incidence of contact dermatitis (i.e., poison ivy dermatitis), and increased susceptibility to cutaneous viral infections, such as *Herpes simplex, Verruca vulgaris, Molluscum contagiosum,* and *Vaccinia.* In vitro experiments also show a decreased lymphocyte response to mitogens (i.e., phytohemagglutinin) and recall antigens (i.e., tetanus) and a defective cytotoxic T-cell response. Reduced chemotaxis of monocytes and polymorphonuclear leukocytes has also been reported in AD. These data indicate that a combination of mechanisms may be important in the immunopathogenesis of AD (Fig. 2).

Role of IgE in AD

Support for an IgE-mediated mechanism in AD is suggested by the following findings typical of AD: elevated serum IgE concentration, positive immediate skin tests and RAST to a variety of food and aeroallergens, association with other atopic diseases (i.e., asthma and allergic rhinitis), and a positive family history for atopy in 80–90% of patients. In addition, bone marrow transplant data have documented the

Immunologic Abnormalities

- Uncontrolled synthesis of IgE with T-cell profile of immediate hypersensitivity (TH_2 cells predominate);
- Decreased delayed hypersensitivity with increased susceptibility to cutaneous viral infections; and
- High spontaneous basophil histamine release.

ability to transfer IgE antibody, specific allergen sensitivity, and AD to previously nonatopic bone marrow recipients. Although the histologic appearance of AD lesions suggest a Type IV, cell-mediated hypersensitivity reaction owing to the cellular infiltrative pattern, recent information on the allergic "late-phase reaction" (LPR) has shown a distinctive cellular infiltrate that is consistent with that seen in AD. Following allergen challenge, IgE-bearing mast cells bind allergen and become activated, releasing cytokines and mediators that perpetuate the allergic response. This "immediate or early" reaction occurs within 15–60 min of allergen challenge and is characterized by erythema, pruritus, and increased capillary permeability. Approximately 4–8 h after the initial allergen challenge, the LPR begins with infiltration of eosinophils, neutrophils, lymphocytes, and monocytes into the site of inflammation. At 24–48 h, lymphocytes and monocytes predominate the cellular infiltrate. This infiltrate seen during the LPR following antigen challenge is similar to the infiltrate noted in the lesions of AD.

Clinical and laboratory correlates have been made in numerous studies in patients with food hypersensitivity and AD. Following positive food challenge, Sampson and colleagues have shown a rise in plasma histamine, without a change in complement activity, basophil number, or total basophil histamine content. Skin biopsy specimens obtained 4 and 14 h after challenge revealed eosinophil infiltrate and deposition of MBP. They concluded that food allergen-induced mast cell activation was shown to trigger both an "early" phase and a LPR in the skin of patients with AD.

IgE molecules have also been found to participate in the inflammatory response via mechanisms other than direct mast cell activation. Sampson has shown that children with AD and food hypersensitivity have high spontaneous basophil histamine release in vitro when compared with normal controls or AD patients without food hypersensitivity. Mononuclear cells from these patients also secreted high levels of HRF. These levels were associated with cutaneous hyperreactivity to a variety of minor stimuli. After an appropriate food elimination diet was implemented for approx 1 yr, spontaneous basophil histamine releasability and production of HRF fell to baseline levels and correlated clinically to less cutaneous hyperreactivity. In addition, passive transfer of this releasing factor could be demonstrated in nonatopic controls. Basophils from nonatopic individuals were stripped of all IgE molecules and sensitized with IgE from food-allergic patients. This rendered the "normal" basophils capable of secreting histamine in response to HRF.

The observation that Langerhans cells and macrophages infiltrating into the dermis of AD skin lesions bear IgE surface molecules provides an important link to understanding the immunopathology of AD. These IgE-bearing cells also express the low-

affinity receptor for IgE (CD23), and presumably function in antigen processing and presentation. Mudde and coworkers demonstrated that in vitro, IgE-bearing Langerhans cells from dust mite-allergic patients were capable of capturing house dust mite allergen for antigen presentation, whereas IgE-negative cells from normal controls or atopic controls who were not dust mite-allergic were unable to capture the allergen. Once activated, these cells have been shown to produce cytokines, such as IL-1 and TNF, that are important in lymphocyte attraction and activation at the inflammatory site. In Mudde's study, IgE-positive cells were shown to activate lymphocytes after specific allergen challenge, whereas IgE-negative cells did not result in lymphocyte activation. In addition to mast cells, these cells likely function as a bridge between initial allergen contact and processing and subsequent lymphocyte activation and perpetuation of the immune response.

Role of T-Cells in AD

The role of T-lymphocytes in the pathogenesis of AD has been the subject of many investigative studies during the last 15–20 yr. The concept that T-cells play a critical role in IgE regulation has been elegantly demonstrated in the murine model. Recently, evidence for this same type of interaction has been found in human studies. Cytokines produced by activated lymphocyte clones regulate the immune response. In the murine model, T helper (T_H) cells are divided into two distinct subpopulations based on the cytokine profile secreted. T helper type 1 (T_H1) cells produce IL-2, IL-3, IL-10, and IFN-γ, and function in cell-mediated immunity responses (i.e., infection and delayed-type hypersensitivity). T helper type 2 (T_H2) cells produce IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, and GM-CSF, and function hypersensitivity responses. These same profiles have been seen in human studies, but with some degree of overlap.

It has been demonstrated that IL-4 acts as an isotype switch factor that commits B-cells to produce IgE. Furthermore, B-cells from patients with AD have been shown to spontaneously produce higher levels of IgE than normal controls. These B-cells also have increased expression of the low-affinity IgE receptor (CD23) on their surface. In vitro data have also shown that IL-4 not only increases IgE production, but upregulates the expression of CD23. Numerous investigators have shown an imbalance in cytokine profiles in patients with AD. These patients typically have a T_H2-like cytokine profile, with increased secretion of IL-4 and IL-5 in particular. Human T-cell clones from such patients demonstrate a decreased production of IFN-γ and increased production of IL-4, resulting in an ability to induce IgE synthesis. This reciprocal relationship between IFN-γ and IL-4 and subsequent induction of IgE synthesis has been documented by several groups. Many have shown that production of IFN-γ or its addition to cell culture will inhibit IgE production and will downregulate the expression of CD23. Van der Heijden and coworkers have also demonstrated a high frequency of IL-4 producing allergen-specific T-cells in lesional skin from AD patients. Van Reijsen noted the same allergen-specific clones from lesional skin with 70% demonstrating a T_H2 phenotype. Both groups suggested that percutaneous sensitization to aeroallergens (e.g., dust mite) may occur and that activation of T_H2-type allergen-specific T-cells may be responsible for the high levels of specific IgE found in 80% of AD patients. These data suggests that atopic patients, and those with AD in particular, have an inability to produce IFN-γ and therefore have a predominance of

Table 3
Differential Diagnosis for AD

Skin diseases
Seborrheic dermatitis
Nummular eczema
Contact dermatitis
Psoriasis
Metabolic disorders
Phenylketonuria
Acrodermatitis enteropathica
Celiac disease/Dermatitis herpetiformis
Immunologic diseases
Wiskott-Aldrich syndrome
Nezelof syndrome
DiGeorge syndrome
SCID
Selective IgA deficiency
Hyper-IgE syndrome
Other disorders
Leiner's disease
Langerhans cell histiocytosis disease

T_H2-type cells, resulting in increased IL-4 production, increased IgE synthesis, and continuation of the allergic immune response.

DIFFERENTIAL DIAGNOSIS

Many types of primary skin disorders, metabolic disorders, and immunologic diseases have associated skin conditions that resemble AD (Table 3). Certain characteristics of these conditions help to distinguish them from AD.

Skin Diseases

Seborrheic dermatitis is the most common skin disorder confused with AD. It is characterized by a greasy yellow or salmon-colored scaly dermatitis that begins within the first few weeks of life, usually before the typical age of onset of AD. Lesions are primarily distributed on the scalp, cheeks, and postauricular areas, but may also occur on the trunk, perineum, and intertriginous regions of the hands and feet. In contrast to AD, significant pruritus is generally not a feature of seborrhea.

Nummular eczema is a disorder characterized by well-circumscribed, circular lesions occurring primarily on the extensor surfaces of the extremities in areas of dry skin. Lesions begin as vesicles and papules that coalesce to form the discrete nonexudative, coin-shaped lesions. Lesions are only mildly pruritic. This disorder is not typically associated with atopy or elevated serum IgE.

Contact dermatitis, both irritant and allergic, can be seen in infants and young children. The skin eruption of irritant dermatitis varies with etiologic agent, but is commonly seen on the cheeks, chin, extensor surfaces of the extremities, and the diaper

area. Irritant dermatitis is typically less pruritic than AD and improves with removal of the irritant, i.e., soaps, detergents, abrasive bedding. Allergic contact dermatitis is characterized by a pruritic, erythematous papulovesicular eruption that involves exposed areas of contact. This dermatitis is uncommon during the first few months of life and can frequently be delineated by a careful history.

Psoriasis is a primary skin disorder that is most commonly seen in older children and adults, but may be seen on occasion in younger children. Fully developed lesions are distinctively different in appearance from those of AD. Lesions are usually erythematous and covered by a silvery scale. Distribution is primarily on the scalp, extensor surfaces of the extremities, and the genital region. Nail involvement is commonly seen with pitting or punctate deformities of the nail surface.

Metabolic Disorders

Phenylketonuria is an inherited disorder caused by an inability to metabolize phenylalanine secondary to a defect in the enzyme phenylalanine hydroxylase. Affected individuals have fair complexion and blond hair. If untreated, seizures and mental retardation result. Approximately 25% of these individuals have an eczematous-like rash associated with their disease.

Acrodermatits enterpathica is a lethal autosomal recessive disorder with clinical symptomatology resulting from profound zinc deficiency secondary to an undefined defect in zinc absorption. The condition is characterized by dermatitis, failure to thrive, diarrhea, alopecia, nail dystrophy, severe gastrointestinal disturbances, and frequent infections. Dermatitis lesions are vesciculobullous and are distributed in a symmetric pattern in the acral and periorificial regions. Treatment of choice is elemental zinc replacement.

Celiac disease is a malabsorption disorder secondary to sensitivity to gliadin, the alcohol-soluble portion of gluten found in cereal grains. An eczematous dermatitis, dermatitis herpetiformis, has been reported to occur in some patients. Dermatitis herpetiformis is a highly pruritic skin rash that is characterized by a chronic papulovesicular eruption on the extensor surfaces and buttocks. This disorder is associated with celiac disease in up to 85% of patients. Treatment for celiac disease is lifelong dietary avoidance of gluten-containing foods.

Immunologic Diseases

Wiskott-Aldrich syndrome is an X-linked disorder characterized by the triad of thrombocytopenia, recurrent infections, and eczema. Patients have impairment of both humoral and cellular immune function. Elevated serum IgE is frequently found. The distribution of the eczematous rash is different from that typically seen in AD and is less responsive to usual medical management.

Nezelof and DiGeorge syndromes are disorders of T-cell immunity. Both have been associated with eczematous rashes and elevated serum IgE concentrations in some patients. The cause of the rash is unknown, but likely associated with the underlying immune dysfunction.

Severe combined immune deficiency (SCID) is a disorder of profound humoral and cellular immune deficiency. Infants frequently present in the first 6 mo of life with failure to thrive, recurrent infections, diarrhea, and dermatitis. Like other immune defi-

ciency syndromes, the eczematous appearing rash is in an atypical distribution and less responsive to conventional therapy.

Selective IgA deficiency is the most common immune deficiency disorder, affecting approx 1 in 400 individuals. It is characterized by decreased mucosal immunity resulting in recurrent sinopulmonary, gastrointestinal, and genitoureteral infections. Some patients remain asymptomatic, whereas others manifest evidence of disease. IgA deficiency may be seen in association with atopic disease in some patients. These patients may develop asthma, allergic rhinitis, or AD. The dermatitis is more typical of AD, both in character and distribution.

Hyper-IgE syndrome is an immune deficiency disorder characterized by markedly elevated serum IgE concentrations in association with recurrent, severe staphylococcal abscesses of the skin and lungs primarily. A chronic, pruritic dermatitis is commonly seen but does not occur in the same distribution or have the same course as AD. Immunologic abnormalities have been found in both humoral and cellular function.

Other Disorders

Leiner's disease (erythroderma desquamativum) is a disorder that usually begins during the first few months of life and is characterized by severe generalized seborrheic dermatitis, intractable diarrhea, recurrent infections (usually gram-negative organisms), and marked wasting and dystrophy. The dermatitis involves an intense erythema of the entire body and extensive large, yellow, greasy scales affecting large portions of the body surface. These scales are desquamative and large skin areas may slough. IgE levels are typically normal and eosinophils are not present. The exact etiology of this disease is unknown, but a familial form exists and has been associated with dysfunction of the fifth component of complement (C5).

Langerhans cell histiocytosis disease is a lethal disorder that is a spectrum of diseases affecting the reticuloendothelial system. A subset of that spectrum, previously known as Letter-Siwe disease, involves a dermatitis that displays features of both seborrhea and AD. The eruption usually begins on the scalp and postauricular areas as a scaly, erythematous rash resembling seborrhea. The rash progresses to involve the trunk with dark, crusted papules that may be associated with petechiae or purpuric papules.

COMPLICATIONS

Infection

Secondary infection of the skin is the most common complication of AD. Infection can be caused by a variety of bacterial, viral, and fungal organisms. The most frequent infections occur with bacterial organisms, most commonly *S. aureus*. As previously stated, some investigators have demonstrated an increased colonization of the skin of patients with AD with over 90% of lesions showing colonization in some patients. These organisms gain access to the deeper skin layers owing to a loss of skin integrity in AD permitting secondary infection. Although *S. aureus* is the most common culprit causing impetiginous lesions, β-hemolytic streptococci are also common. Infected skin lesions may be difficult to detect owing to the similarity of appearance between chronic AD and secondary infection. Infected lesions may appear more erythematous, pruritic, and crusting with areas of open excoriations. Deep pyogenic infections, such as furun-

cles, abscesses, and cellulitis, are unusual in AD. Systemic antibiotics are the treatment of choice and frequently provide significant relief of symptoms and aid in clearance of skin lesions.

Viral infections are a particularly troublesome complicating factor in some patients with AD. Patients have an unusual susceptibility to certain types of viral infections. The most common organisms found are *H. simplex* (eczema herpeticum), *V. vulgaris* (common warts), *M. contagiosum*, and *Vaccinia* (eczema vaccinatum). Kaposi's varicelliform eruption is a particularly severe, explosive infection caused by herpes simplex or vaccinia infection. Viral lesions are typically vesiculopustular in appearance and occur in clusters on both affected and unaffected skin, but with a predilection toward affected skin. The lesions of molluscum contagiosum are papular, centrally umbilicated lesions surrounded by a pale halo. All viral lesions can be seen on any portion of the body. Infection may be localized or result in systemic toxicity (i.e., herpes and vaccinia). Appropriate antiviral therapy may be indicated on a long-term basis to combat these infections, some of which can become latent and recur later (i.e., herpes simplex). In addition to the mentioned viral infections, patients with AD may be at increased risk for developing severe infection following exposure to varicella.

Fungal infections can also complicate the course of AD. *Trichophyton rubra* and *P. ovale* or *P. orbiculare* are the most commonly implicated organisms. *Candida albicans* has also been implicated in some reports, but strong evidence for it being a source of infection does not exists at present. Infection with *P. ovale/orbiculare* is typically seen in the adolescent or adult patient with AD in whom a typical head and neck distribution of lesions is noted. Topical and systemic antifungal agents may be necessary to control infection.

Ocular Conditions

Ocular abnormalities may be seen in patients of all ages with AD. The most common and potentially severe complication is the development of anterior subcapsular cataracts in some patients with AD. The incidence has been reported to be between 5 and 16% with most cataracts occurring between 10 and 30 yr. Rarely posterior subcapsular cataracts may occur, but this is more commonly seen in the patient requiring systemic corticosteroid therapy.

Other ocular conditions seen in association with AD include conjunctivitis, keratitis, and keratoconus (elongation of the corneal surface). Conjunctivitis is frequently a year-round complication of AD, but may also be seen in a seasonal distribution in association with allergic rhinitis in patients with aeroallergen hypersensitivity. Vernal conjunctivitis, characterized by a "cobblestone" pattern of papules on the inner eyelid, may be especially troublesome requiring prompt treatment to prevent corneal abrasion. The association of AD and keratoconus is unexplained, yet of concern in approx 1% of patients with AD. Corneal erosions may also be seen in patients with secondary herpetic infections that go undiagnosed and untreated.

Skin Conditions

Pityriasis alba and keratosis pilaris are two benign skin conditions that are commonly seen in patients with AD. Pityriasis alba is characterized by patchy areas of depigmentation of the skin, primarily occurring on the face and extensor surfaces of the extremities.

Key Features of Therapy

- Treatment should involve a variety of approaches, including avoidance of irritants and allergens, general skin care measures, and medication;
- It is highly important to control pruritus;
- Topical corticosteroids are the cornerstone of pharmacologic management; and
- Control of skin infections is essential.

Keratosis pilaris is a follicular hyperkeratosis characterized by fine papular lesions surrounded by dry skin that primarily occur on the buttocks and extensor surfaces of the upper arms and thighs. Both conditions may be seen in other skin disorders and in patients with otherwise normal skin. Their etiologies are unknown, but both remain only as benign nuisances.

TREATMENT

At present there are no known cures for AD, and current therapy is largely symptomatic. Certain therapeutic measures can be instituted that will dramatically reduce symptoms and control the overall skin condition (Table 4).

Environmental Control

Environmental control measures, both in the form of minimizing allergen exposure and pruritic stimuli, should be instituted in all patients with AD. Minimization of extreme fluctuations of temperature and humidity results in less pruritus. Sweating will induce pruritus in many patients with AD; therefore, a moderate temperature environment should be maintained. Clothing should be loose and free of wool. Cotton fabrics are generally the best tolerated. Coarse fabrics in clothing and bedding should be avoided. Complete rinsing of detergents, soaps, and bleach from clothing and bedding will also minimize their irritant potential. Occupational avoidance of aggravating agents, such as chemicals, irritants, and solvents, should be performed by older patients with AD. Minimization of emotional stress will also lessen the potential for pruritus.

Avoidance of known aeroallergens should be instituted when possible. The most easily avoided allergens are dust mites and animal danders. Dust mite-sensitive patients should institute full dust mite avoidance procedures consisting of the following: plastic or hypoallergenic covers encasing mattresses and pillows, removal of all feather pillows and stuffed animals from the patient's room, frequent high-temperature washing of the bedding, and removal of carpeting and draperies from the patient's room when practical. Animals (especially cats and dogs) should be removed from the home and contact should be minimized. Practical avoidance of other aeroallergens (e.g., avoidance of cut grass) should be attempted.

Dietary Restriction

In patients with food hypersensitivity, food allergen avoidance results in improvement of AD. Sampson and coworkers have shown that by following a strict avoidance diet of relevant food allergens patients experience symptomatic relief of pruritus and

Table 4
Treatment for AD

Environmental control
Climatic control
Nonabrasive clothing and bedding (cotton)
Minimization of emotional stress
Avoidance of irritants
Avoidance of aeroallergens
Dietary control
Food allergen restriction
Skin care
Minimization of trauma
Avoidance of harsh soaps/detergents
Hydration
Lubrication
Antipruritics
Hydroxyzine
Diphenhydramine
Corticosteroids
Topical
1% Hydrocortisone ointment to facial lesions
Medium-potency ointment to body lesions
Systemic (rare use only)
Tar preparations
Antibiotics
Antistaphylococcal/antistreptococcal
Antifungal (rare use only)

clearing of skin rash. Owing to the high false-positive rate of prick skin testing and RAST for food allergens, an elimination diet followed by a blinded (single- or double-blind) or open food challenge should be performed to confirm clinical reactivity to a particular food, unless a convincing history of anaphylaxis is obtained. Extensive elimination diets should not be prescribed on the basis of skin test positivity alone owing to the obvious nutritional complications. The period of dietary restriction is allergen-dependent, but generally should occur for 1–2 yr before reintroduction or rechallenge with the implicated food.

Skin Care

General measures to reduce skin trauma owing to scratching should be instituted. Appropriate bedding and clothing can help minimize itching. In infants and children, gloves and socks can be used to reduce scratching, especially during sleep. Fingernails should be trimmed to minimize skin trauma from scratching.

Skin hydration is an extremely important measure in controlling the rash and pruritus associated with AD. Although some clinicians feel that frequent or routine bathing is contraindicated in AD, may others institute frequent bathing as part of the treatment protocol. Bathing hydrates the chronically dry skin of AD and may reduce the likelihood of bacterial superinfection, both of which will reduce pruritus and activation of le-

sions. In addition, swimming has long been recognized by patients with AD as a soothing therapy. Patients should bath in lukewarm water for 30 min once or twice a day (depending on the severity of disease). Burrow's solution, oatmeal, or oils (i.e., Alpha-Keri) may be added to the bath water to reduce pruritus further. Hydrating body wraps with water-soaked towels may be used in addition to bathing to maximize hydration of severely affected areas. Showers are inadequate in the management of AD owing to the lack of hydration obtained. Mild soaps (i.e., Dove or Basis) should be used for cleansing. Harsh soaps may be drying and serve to increase pruritus.

Lubricants should be applied to the skin immediately following bathing and other times during the day with a twice daily minimal application. Lubricants will counteract dryness and "seal in" the hydration obtained from the prolonged bathing experience. Lubricants should be free of alcohols and perfumes, both of which can be irritating and drying. Effective lubricants include Vaseline, Unibase (oil in water preparation), Eucerin, or Aquaphor (water in oil preparations), plus others.

Antipruritics

Of major importance in the successful treatment of AD is interruption of the itch-scratch cycle. In addition to the methods mentioned previously, antihistamines and occasionally sedatives provide valuable relief of symptoms. Hydroxyzine (2 mg/kg/d divided every 6 h or given at bedtime; maximum adult dose 600 mg/d) and diphenhydramine (5 mg/kg/d divided every 6 h or given at bedtime; maximum adult dose 400 mg/d) have been shown to reduce itching dramatically and reduce sleep disturbance in patients with AD. In young children with severe disease, short-term sedation with chloral hydrate (50 mg/kg/d given at bedtime) may be needed until control of symptoms can be obtained. Topical application of Doxepin cream also provides relief of pruritus, but poses a greater risk for side effects owing to its systemic absorption. Doxepin should be used with close observation in all patients, especially children and patients with large skin surface areas affected.

Corticosteroids

Corticosteroids are used in AD to control inflammation. These preparations are very effective in controlling skin lesions of AD, but should be used wisely. Systemic corticosteroids do not play much of a role in the management of AD, except in the most severe cases. When used, oral corticosteroids should be prescribed for only a limited time period and should be tapered judiciously. Patients will typically clear quickly with the use of oral corticosteroids, but frequently relapse once their use is discontinued. In addition, the side effects associated with use of systemic corticosteroids are well known and generally preclude their use.

Topical corticosteroid use in AD is the mainstay of therapy. The potency of topical steroids used is dependent on the severity of skin disease and the location of skin lesions. In general, topical steroid potency is related to the vehicle and the chemical preparation. Gel preparations penetrate more effectively, but are drying and therefore not of great benefit in AD. Ointments penetrate well and enhance hydration, but feel occlusive and may be poorly tolerated during periods of high temperature (i.e., summer). Creams and lotions are less potent and penetrate less effectively than gels or ointments, but are more comfortable to some patients. Except in mild cases, ointments should be

used because of their higher penetrance and potency. The lowest strength that gives adequate results should be used. Halogenated corticosteroid preparations, such as 0.1% betamethasone (Valisone), 0.025% flucinolone (Synalar), and 0.1 or 0.025% triamcinolone (Aristocort, Kenalog), have potent anti-inflammatory properties and can be used sparingly on affected body lesions. These preparations should not be used on the face. Hydrocortisone cream or ointment (1%) can be sparingly used on the face, but the use of stronger preparations should be avoided. Topical steroids should be applied twice daily after application of lubricating creams or ointments as discussed. These preparations will penetrate the lubricant and reach the affected skin. Although generally safe from systemic absorption, diffuse application of topical steroids over long periods of time can have the adverse effects of striae, atrophic thinning of skin, ulcerations, hirsuitism, acne, and telangectasia. In addition, cases of adrenal suppression secondary to topical steroids have been reported. Although these complications are rare with prolonged use of low-potency topical steroids, their use in children and adults with severe disease should be monitored.

Tar Preparations

Coal tar preparations have been used for many years in the management of AD. Although topical corticosteroids have generally replaced the routine use of these keratolytic agents, they are still effective in the management of chronic, lichenified skin lesions that respond poorly to corticosteroids. The mechanism by which coal tar preparations work is unknown, but clinical evidence has shown that they have both anti-inflammatory and antipruritic effects. These preparations are will tolerated, but prolonged use may lead to folliculitis and photosensitivity. Shampoos containing tars are especially useful in the patient with scalp involvement, i.e., as in both AD and seborrhea.

Antibiotics

As previously stressed, patients with AD have a high degree of bacterial colonization of both affected and unaffected skin. The risk and occurrence of bacterial superinfection of the AD skin is therefore high, most commonly with *S. aureus* and streptococcal organisms. In addition, Leung and others have shown that some patients with AD produce specific IgE antibodies to various exotoxins produced from *S. aureus*. Because of these factors, antistaphylococcal and antistreptococcal antibiotics should be used liberally in the AD patient with documented or suspected bacterial superinfection. Skin cultures can be helpful in documenting the type of organism present and the antibiotic sensitivities of the organism. From a clinical standpoint, all patients with exudative, crusted, or excoriated lesions should raise the clinical index of suspicion for secondary bacterial infection. Appropriate antibiotic therapy should be instituted for 10–14 d. In cases of limited distribution of infected skin lesions, topical antibiotic therapy with preparations, such as Bactroban ointment, may be adequate. For most cases, systemic antibiotics will be required to eradicate the infection. Increased skin care regimen with more frequent bathing may also help to reduce the bacterial load.

A few reports have addressed the issue of secondary infection caused by fungal infections, such as *P. ovale*. These investigators have advocated the use of topical agents

to fight fungal growth, such as use of Sebulex or Selsun shampoo. Others have recommended the use of oral antifungal agents when fungal organisms are documented or highly suspected. Experience to date is relatively empiric and not well established.

Phototherapy

UV light therapy with UV-A rays has been offered to some AD patients for control of lesions. Rajka has reported favorable results in a small series of AD patients when phototherapy was provided to eczematous skin lesions and maintenance therapy was sustained. This method of therapy has been proposed for the patient who is poorly responsive to conventional therapy or in whom severe AD is present. Rajka also notes that phototherapy may be beneficial in children with severe disease requiring systemic steroids to reduce the potential side effects of long-term coriticosteroids. Most commonly, UV therapy must be given at least weekly and sustained over long periods of time to prevent relapse. This regimen raises the issue of adverse effects of long-term UV light exposure, such as induction of malignancy and chronic skin changes. Most clinicians feel that the risk/benefit ratio is too high to encourage this form of therapy for the average AD patient. Phototherapy should therefore be reserved for the complicated patient who is poorly responsive to other forms of therapy.

Immunotherapy

Although allergen immunotherapy has been useful in some atopic conditions (i.e., allergic rhinitis), its role in the treatment of AD has been limited. In clinical practices, immunotherapy will frequently exacerbate the condition of AD rather than provide relief. Some clinicians advocate the use of immunotherapy, especially in older patients with significant aeroallergen hypersensitivity, but recommend initiating therapy with a much smaller dilution of allergen extract than would be performed in standard therapy for allergic rhinitis. The dose of extract needed to induce tolerance is often greater than the dose tolerated by the patient with AD, thereby precluding its use in most patients.

Immunomodulatory Therapy

As previously discussed, AD is associated with abnormalities of the immune system, especially with regard to cytokine production and IgE regulation. In particular, many investigators have shown a predominance of T_H2-type lymphocytes, which produce excess amounts of IL-4 and therefore upregulate IgE production. These patients are noted to have little IFN-γ production in comparison. Some of these same investigators have also shown that IFN-γ suppresses IgE production in vitro and has effects on immune effector cell function. A recent, double-blind, placebo-controlled, multicenter trial was conducted to examine the effects of recombinant IFN-γ (rIFN-γ) administration to patients with chronic AD. Patients treated with rIFN-γ had a significant reduction in symptoms and a mean reduction in circulating eosinophils when compared to the placebo-treated group. A previous trial of 23 patients also showed a significant fall in IgE synthesis in rIFN-γ-treated patients. These studies provide examples of potential immune modulatory therapy that will likely become of more importance in the future as our understanding of the immunopathogenesis of AD expands.

Psychotherapy

AD is a very aggravating chronic disease that can be emotionally challenging for patients and families alike. Emotional distress and problems can trigger episodes of pruritus and worsen the AD condition. In addition, young patients and their families may have difficulty understanding and coping with this chronic condition and may need help to establish parameters for discipline without adding to the emotional tension of an already aggravated child. Older children and adolescents may also experience body image problems related to the obvious skin abnormalities. For all of these reasons, some patients and their families will benefit from social service support and/or psychological counseling to address these issues. This is particularly important in the severe, chronic patient.

PROGNOSIS

Currently there are no prospective, longitudinal studies evaluating the prognosis and disease remission of AD. Vickers retrospectively evaluated 2000 children with AD after 20 years and noted an overall clearance rate of 84%. Vowles likewise evaluated 84 patients after 13 years and found only 45% resolution of disease. These and other studies reflect the difficulty in assessing prognosis with reports of disease resolution ranging from 37 to 84% in various retrospective surveys. In addition, no specific disease factors are predictive of the disease severity or course. Some patients are noted to have spontaneous resolution of their disease during infancy and early childhood. Improvement may also be seen during puberty in some patients, but exacerbations noted in others. Adults will often resolve or significantly improve after the second decade of life. As is common with atopic diseases, some patients resolve their AD but develop other forms of atopy, such as allergic rhinitis and asthma. Until a well-designed, prospective, longitudinal survey of AD is conducted, predictions of disease outcome will remain purely speculative and based on clinical experience. These factors reiterate the need for consistent long-term follow up and management to serve best the needs of patients with AD.

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14 Contact Dermatitis and Other Contact Reactions

Jere D. Guin, MD

CONTENTS

WHAT IS CONTACT DERMATITIS?

Contact dermatitis typically is an eczematous reaction, usually to a substance applied to the skin surface. It may have an allergic cause, or it may be irritant (nonallergic). The archetype of the allergic form is poison ivy dermatitis, whereas soap dermatitis is a typical example of irritant contact dermatitis. Of course, there are many forms of allergic contact dermatitis that differ prominently from poison ivy reactions, and irritant dermatitis is extremely diverse in cause and often in presentation. Both irritant and allergic contact dermatitis are very common. They often complicate other forms of eczema, which can be confusing to the inexperienced. However, recognition is critical to the success in managing such patients.

Irritant reactions are caused by (nonimmune) damage to cells in the epidermis from a variety of stimuli ranging from physical agents, such as friction, cold, and sunburn, to chemical reagents, such as acids, bases, organic solvents, and so on. The subject is quite complex, since the specific injury varies, and individuals may be exposed to multiple ir-

From: *Allergic Diseases: Diagnosis and Treatment*
Edited by P. Lieberman and J. Anderson Humana Press Inc., Totowa, NJ

Key Features of Contact Dermatitis

- Contact dermatitis can be immune- or irritant-induced.
- Contact dermatitis is recognized in great part by its distribution.
- An eczema that fails to heal should suggest contact dermatitis.
- The appearance of contact dermatitis can range from an weeping, oozing lesion in the acute phase, to a thickened, lichenified rash in its chronic stages.
- Patch testing is the test of choice to identify the offending agent.
- Avoidance is the treatment of choice.

ritants in many occupations as well as at home. Basically agents that cause contact dermatitis on a basis other than allergy are by definition irritants. In occupationally induced contact dermatitis, irritant reactions account for about 70% of the total.

Allergic contact dermatitis is a delayed hypersensitivity response mediated by T-cells, with Langerhans cells as the characteristic presenting cells. The number of cytokines and cell types involved in regulation of the response is beyond the scope of this chapter. For a more detailed explanation, *see* Chapter 1.

Other "contact" reactions include allergic and nonimmunologic contact urticaria, photoallergic and phototoxic dermatitis, protein contact dermatitis, and systemic contact dermatitis, including some id reactions and some cases of dyshidrotic eczema.

Photoallergic dermatitis is essentially an allergic contact dermatitis where the antigen must be activated by light, whereas phototoxic reactions are equivalent to light-induced irritant dermatitis. The former tends to be eczematous, whereas the latter frequently resembles a severe sunburn. Both are located in sun-exposed sites.

Contact urticaria may be either allergic (IgE-mediated) or nonimmunologic where a wheal occurs through inflammation without allergy. An example of the former is hives appearing on the hands of a chef allergic to shrimp, following the peeling of shrimp. An example of the latter is the erythema and swelling seen after local exposure to dimethyl sulfoxide or Trafuril.

HOW DOES ONE RECOGNIZE CONTACT DERMATITIS?

1. The first prerequisite for recognizing contact dermatitis is to suspect it. One should always consider the possibility of a contact reaction in anyone with eczema. Even noneczematous conditions may have a contact reaction superimposed on the pre-existing condition.
2. The eruption is typically eczematous, and as such, it will normally show spongiosis histologically. Acute lesions demonstrate weeping, oozing, crusting, and scaling, and chronic lesions tend to show thickening, hyperkeratosis, lichenification, and scratch papules.
3. The pattern is man-made. A good example is glove dermatitis (Fig. 1). Here one usually sees eczema involving the palms and dorsum of the hands with a sharp cutoff above the level where the gloves are worn. Another suggestive picture is earlobe dermatitis (Fig. 2) where the ears have been pierced and where a weeping, oozing, crusting, and itching eruption surrounds the puncture site.
4. A recognizable pattern may be present. This is often learned by experience, but almost all physicians in the United States recognize poison-ivy dermatitis (Figs. 3–5) with its

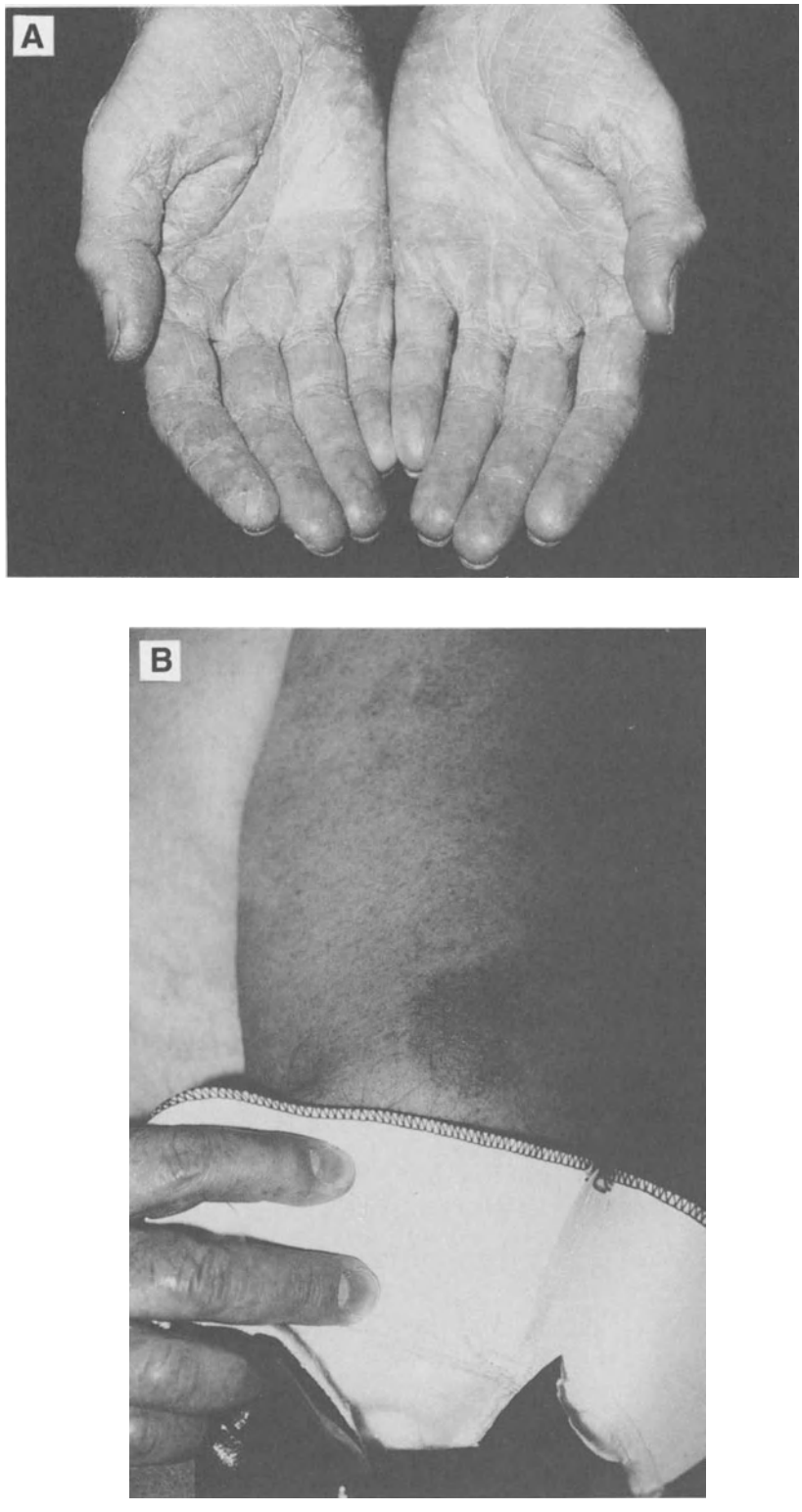

Fig. 1. (**A**) Glove dermatitis from rubberized work gloves. (**B**) Positive patch test to a piece of the glove.

characteristic streaks caused by finger strokes and handprints. Insole dermatitis to shoes (Fig. 6) characteristically involves contact sites on the plantar surface with sparing of the longitudinal arch and proximal toes and accentuation of pressure sites, such as over the metatarsal heads and the tips of the toes. In one case, the allergen is transferred from the hands, and in the other, the eruption is seen where the causative object touches the skin (*see also* Fig. 7). One must be careful, however, in trying to identify a cause by pattern alone, since experts are often fooled. Therefore, patch testing is used for confirmation.

5. Eczema that fails to heal with treatment should make one suspect contact dermatitis. Those of us who subspecialize in contact dermatitis see this regularly. Sometimes the original problem is no longer present, and the patient proves to be allergic to a cosmetic lotion or topical medication he or she applied to soothe the original dermatitis (Figs. 8, 9). Sometimes one sees a typical medication pattern with eczema spreading around lesions from the applied substance with fewer lesions at the periphery where less has been applied. In some cases of milder sensitivity, and especially corticosteroid allergy, one may see the original condition unchanged, but refusing to heal.
6. There is often a previous history of contact allergy or irritation. For example, one might look for contact dermatitis to an aminoglycoside in a nurse with a previous allergy to neomycin.
7. A known allergy, irritation, or predisposing condition is present. Atopics of all types typically are susceptible to certain irritants, e.g., soaps or propylene glycol. Persons with stasis dermatitis and chronic allergic contact dermatitis often develop sensitivity to agents used on the eruption.
8. There is often a history of the use of multiple agents, either prescribed or OTC. This is especially true in stasis dermatitis.
9. There may be a history of high-risk exposure, which is often associated with occupation or avocation. Hospital aides commonly develop irritant dermatitis from bathing patients, shampooing patient hair, scrubbing rooms, and so on. Dishwashers commonly develop irritant hand eczema. Construction workers are more likely to develop chromate allergy from exposure to cement and mortar. In some occupations, exposure is a complex mixture of irritation and allergy not only to substances found on the job, but also to materials used for treatment and putative protection. For example, beauticians develop irritant dermatitis from shampoo and allergic contact dermatitis from glyceryl monothioglycolate in acid perms and *p-phenlyenediamine* in hair dye. They then commonly become allergic to the gloves used to try to protect their hands so they can continue to work!

HOW DOES ONE SEPARATE IRRITANT FROM ALLERGIC CONTACT DERMATITIS?

This can be a very sticky, yet practical problem. There are no absolute rules, so one must use the weight of the evidence. Some helpful criteria are found in Table 1.

Irritant reactions tend to occur often within minutes, burn rather than itch, and heal rapidly on avoidance. Irritant patch test responses typically are evident within a few minutes, although they may be cumulative or even delayed. They are often somewhat dose-related, disappearing on dilution. They are often sharply marginated, and they occur on first exposure so that prior sensitization is unnecessary. Irritant reactions from soap, detergents, and solvents are often shiny, dry, and fissured.

Allergic contact dermatitis tends to itch more reliably than irritant dermatitis (but there are exceptions); the reaction may spread for days after the allergen has been re-

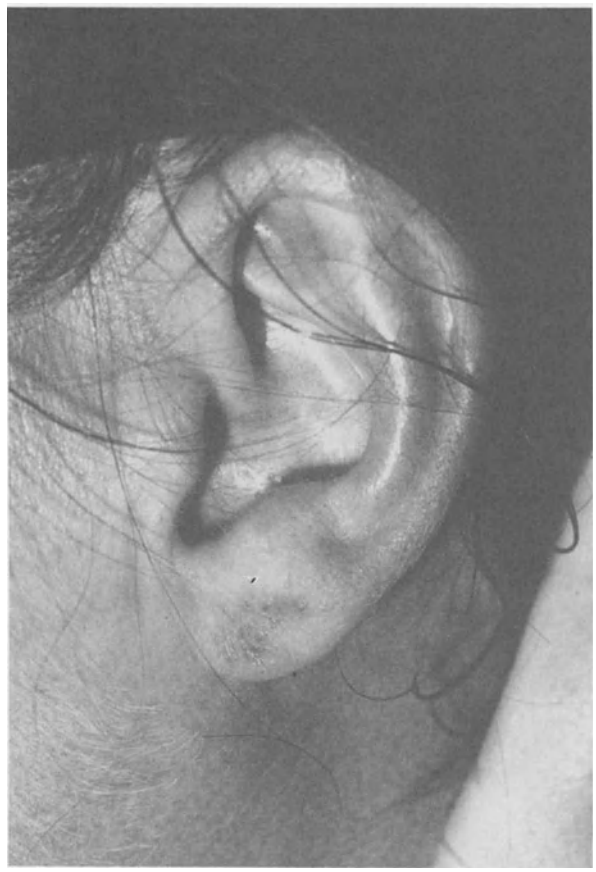

Fig. 2. Earlobe dermatitis in a nickel-sensitive individual. The nickel spot test is helpful here since it allows the patient to test jewelry for free nickel before it is worn.

moved; it is also less dose-related; it occurs in susceptible persons (not everyone breaks out to even poison ivy), and it requires prior sensitization. Allergic contact dermatitis typically appears after 36–48 h, but can be earlier with strong allergy or in sites where absorption is rapid, e.g., the face.

Putative histologic differences, and even sophisticated cytokine studies have recently been questioned so it may be difficult to separate irritant and allergic contact responses histologically. Patch testing may uncover unsuspected allergy in one who seems to have irritant dermatitis. Negative patch test results (sometimes wrongly) suggest an irritant cause. Reactions suggesting an irritant cause can be confirmed by serial dilution, since irritation more often disappears sharply with decreased concentration. Some persons have both irritant and allergic contact dermatitis at the same time. Sensitization commonly occurs from irritants and many allergens, e.g., poison ivy, are both irritant and allergic. Furthermore, the already tender skin from either cause is more susceptible to the other as a secondary event. **It is wise to have persons with irritant dermatitis avoid known allergens, and those with allergic contact dermatitis avoid irritants.**

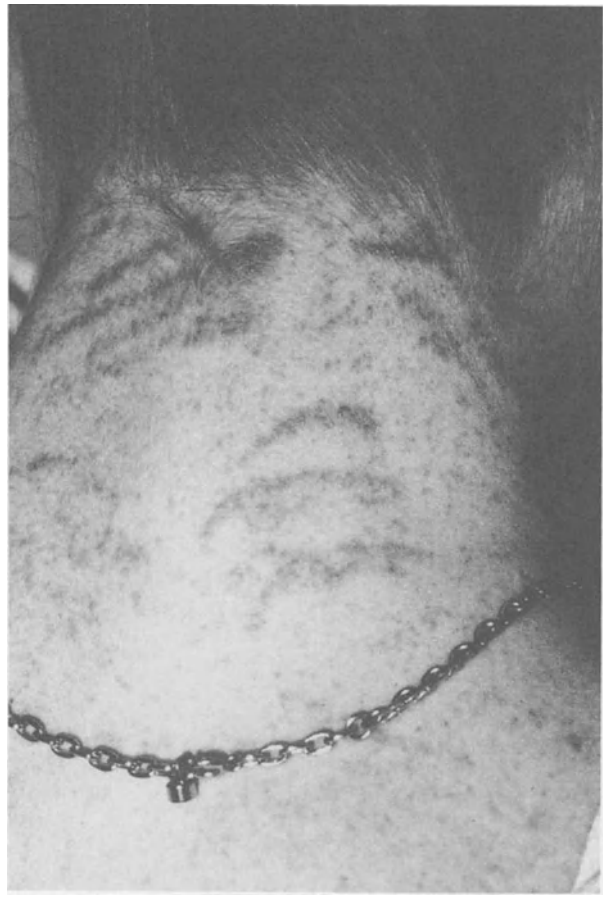

Fig. 3. Classic streaks of poison ivy dermatitis. This pattern is caused by hand transfer of a strong antigen.

HOW CAN ONE SEPARATE CONTACT DERMATITIS FROM OTHER DERMATOSES IN DIFFERENT ANATOMIC SITES?

Contact dermatitis can mimic many other skin conditions. A reasonable listing that can be used in the differential is given in Table 2. The differential in certain regions, especially the hands, deserves a bit more explanation.

The Hands

Hand eczema is a very special problem because the patient commonly has more than one cause for the eruption. Contact dermatitis of the hands is often irritant with dry scaly patches, which in some atopics are converted to a discoid eczema. Dermatitis under a ring is usually an irritation from soap. Occupational factors are important, since persons handling raw meat (slaughterhouse, chicken processing, and fishery workers, butchers, and chefs, for example), those engaged in wet work, and mothers with small children

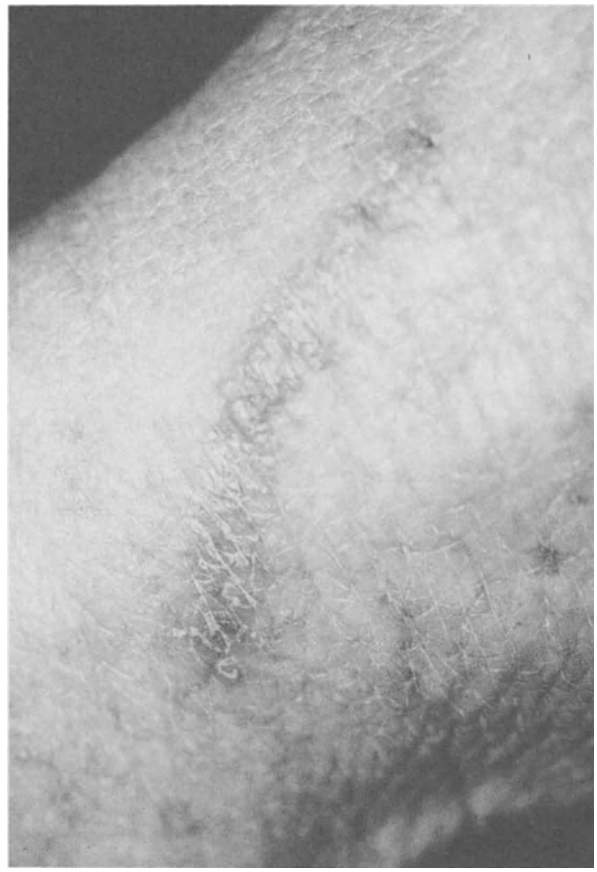

Fig. 4. Streak of poison ivy dermatitis.

are particularly vulnerable. Another often unsuspected cause is in mechanics, machine repairmen, and so forth, who try to remove insoluble metal dust, carbon, and rubber dust with soap and abrasives, irritating the skin in the process. Often a nonsensitizing cream will remove such materials without irritation. Allergic contact dermatitis is covered in the (next) section on regional contact dermatitis.

Persons with a nummular or discoid pattern (Fig. 10) are often atopic individuals. Sometimes women who had atopic eczema as children but who have enjoyed a prolonged remission break out anew from the stress of wet work and irritant exposure with the rearing of children.

Dyshidrotic eczema or pompholyx (Fig. 11) is identified morphologically by its deep-seated single vesicles (at least initially), and the tendency for the vesicular eruption to form an apron pattern. It is commonly a dermatophytid, but systemic contact dermatitis, stasis eczema with id, infectious eczematoid dermatitis, nummular eczema, or other causes can often be found if one looks carefully. Some cases are, however, idiopathic.

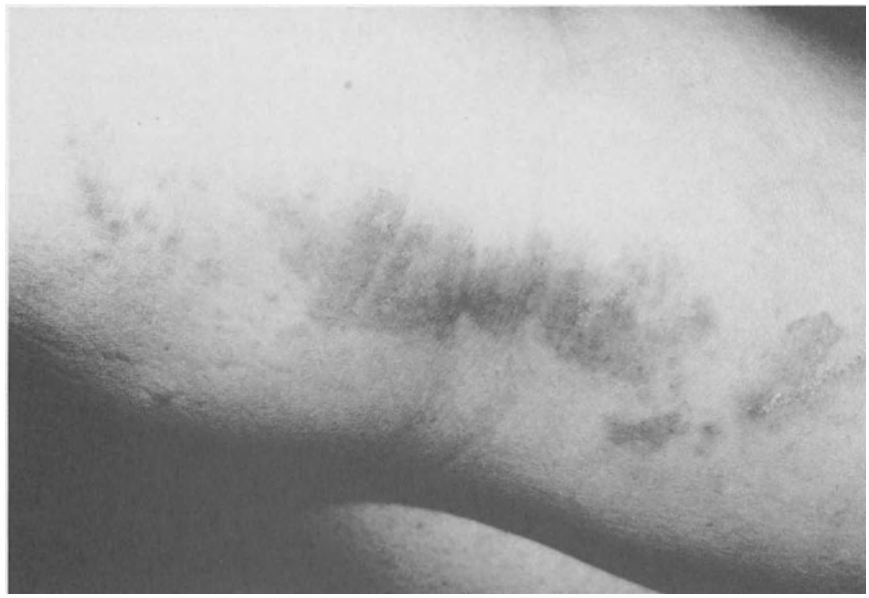

Fig. 5. Poison ivy dermatitis.

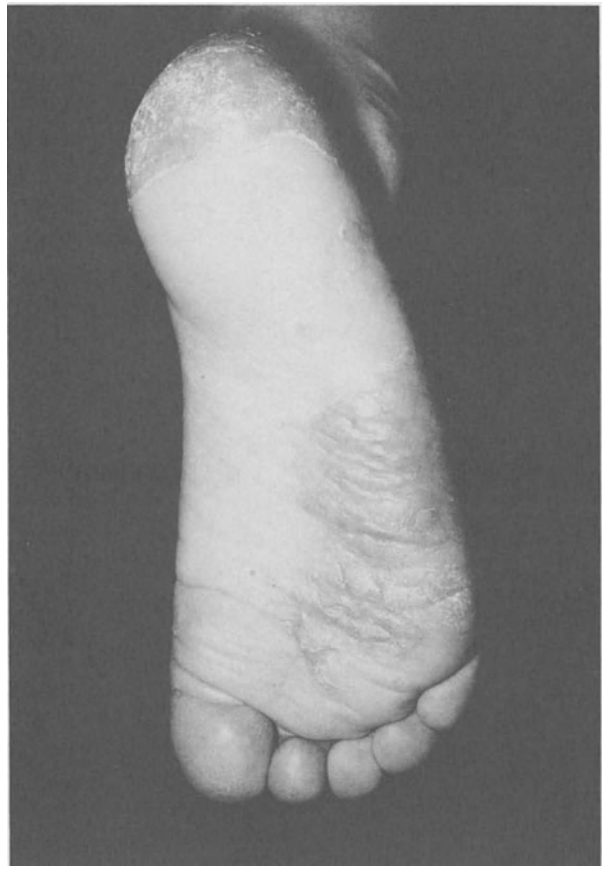

Fig. 6. Six-year-old girl with contact dermatitis to shoes. She reacted to potassium dichromate on patch testing, suggesting leather as a source.

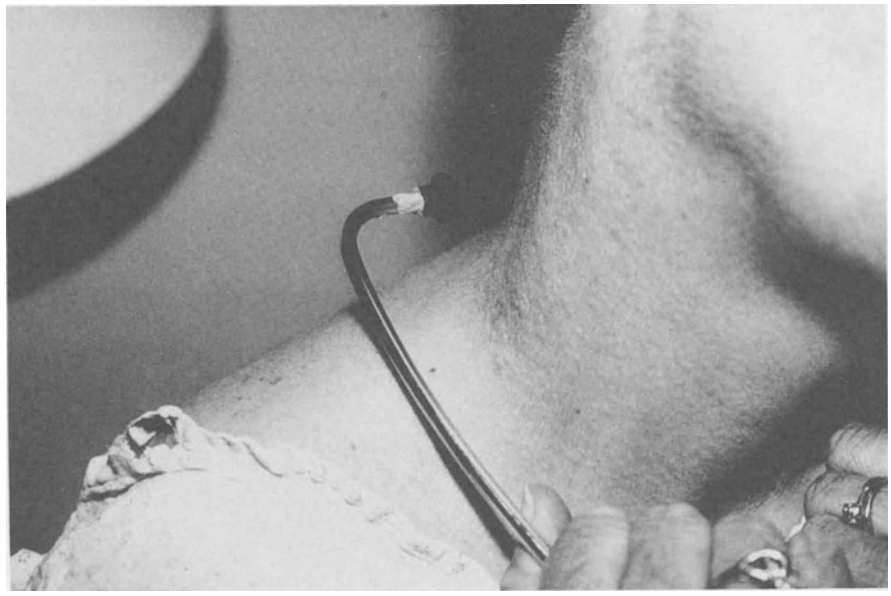

Fig. 7. Nickel sensitivity to metal tubing of a stethoscope.

Hyperkeratotic hand eczema may occur from contact dermatitis. When it does, it is often difficult to know whether one is faced with one or more than one condition. Perhaps the main things to rule out are certain skin diseases that characteristically occur in areas of trauma. This is often called the Koebner phenomenon in psoriasis, lichen planus, and so on. On the fingers and palms, psoriasis is often misdiagnosed as eczema, because it is located in areas of contact, such as the thumb, index, and middle fingers, along with frictional areas of the palms. Psoriasis in this location usually does not itch, it fissures in winter, and is usually associated with other findings characteristic of psoriasis, such as pitting of the fingernails, onycholysis, and lesions of the elbows, knees, scalp (especially in the nuchal area), and in the intergluteal fold. A positive family history should make one suspicious, but it is often negative. Lichen planus can also be located on the hands. Lesions of that disease elsewhere are usually more typical in morphology, and unlike most cases of psoriasis, a biopsy can be helpful. Certain drugs are often aggravating factors in psoriasis and lichen planus and may be the cause of the latter.

Lesions on the hands (and feet) can also be caused by infectious and parasitic agents, including dermatophytosis, scabies, and herpes simplex, which can all on occasion mimic contact reactions. The morphology and distribution help, and a KOH, Tzanck, and/or culture will confirm the diagnosis.

On the hands, allergic contact dermatitis is suspected especially when the grip and frictional areas of the palms are involved, but patch testing can be justified in most patients with hand eczema, since it helps establish the cause. A glove-like pattern is a giveaway for glove dermatitis. This is usually caused by rubber, but it can also occur

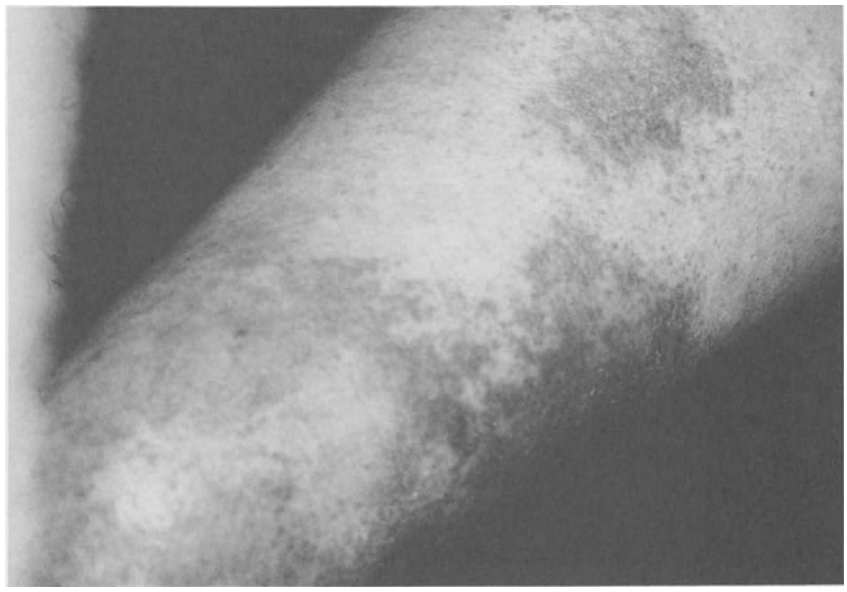

Fig. 8. Eczema that seems to spread where an ointment or lotion is applied suggests sensitivity to a medication. Patch testing was positive to neomycin, which was a component of the cream she had applied.

from leather and other materials. Occupational patterns (Fig. 12) are often seen in the grip areas of the fingertips in florists from Alstroemeria, in chefs from garlic, in hairdressers from glyceryl monothioglycolate in acid perms, and in industrial workers from epoxy and other adhesives, to name a few. Sometimes a pattern can suggest a source, as with liquid soaps, which cause an eczema of the finger webs extending onto the palm at the base of the middle and adjacent fingers. Sometimes the contact dermatitis alters the appearance of the original condition, such as the fingertip eruption one sees from shampoo (which may be irritant or allergic), or the spreading eczema, which occurs from reactions to medications. A diffuse dermatitis of the dorsum, sparing protected areas, may be light-induced. Remember, however, even typical presentations require patch-test confirmation.

Flexural Areas

In intertriginous areas, contact reactions are often from topically applied agents. Inframammary eruptions can be from the bra, especially from rubber chemicals. In the hairy part of the axillae one must rule out deodorant ingredients, whereas in the periaxillary area clothing dermatitis may be present. In the differential, various causes of intertrigo may be confusing, including candidiasis, seborrheic dermatitis, seborrheic psoriasis, tinea, and gram-negative superinfections. Hailey-Hailey disease is a familial condition inherited as autosomal-dominant, and located usually on the neck, and in the axillae or the groin. Here a biopsy will make the diagnosis, and the family history is often positive.

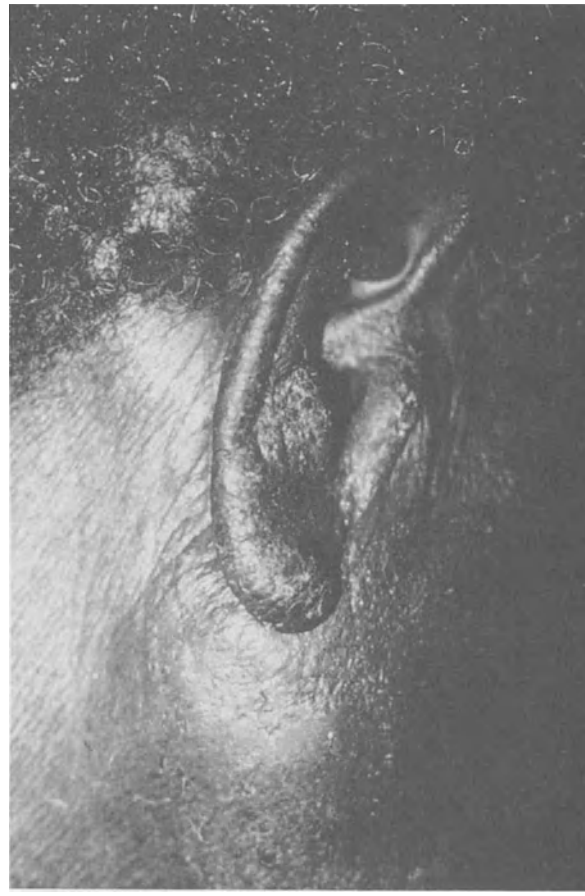

Fig. 9. Depigmentation following a reaction to ear drops containing neomycin. This patient was allergic to multiple aminoglycosides, but not to streptomycin, which lacks the 2-deoxystreptamine ring.

The Elbows and Knees

Over the elbows, rubber dermatitis, topically applied lotions, OTC and prescribed medications, and clothing should be suspected. One must, of course, consider anything on which the patient might lean. I have seen nickel-induced eczema in this location from metal contact, and even poison ivy-like dermatitis has occurred from furniture lacquered with the Japanese lacquer tree, a relative of poison ivy. In the differential, psoriasis, dermatitis herpetiformis, frictional lichenoid eruption (in children), Gianotti-Crosti syndrome, and papulovesicular acrolocated syndrome should come to mind, among other things. Systemic contact dermatitis and id reactions may also appear here.

The Scalp

The scalp usually is not prominently involved even when hair-care products cause allergic contact dermatitis, since the hair is protective. However, one can see scalp in-

Table 1
Differentiating Allergic vs Irritant Contact Dermatitis[a]

	Allergic	*Irritant*
Appearance	Redness, vesicles, papules, oozing, crusting, lichenification	Redness, chapping, scaling, fissures, pustules
Population involved	Sensitive individuals (only one person at this job)	Anyone with adequate dosage (many doing the same job)
Onset following exposure	Varies with location (usually days)	Minutes to hours, but may be cumulative
Requirement for previous exposure	Yes	No
Dose dependency	Less	More Dilution tends to abolish the reaction
Typical symptomatology	Itching	Burning, pain
Localization of patch-test response	May spread beyond application site after removal of chamber	Often sharply marginated, limited to occluded area
Patch test, relevance	Positive and relevant	Negative or positive and not relevant

[a]Irritant and allergic reactions often coexist and can be difficult to separate reliably clinically or histologically. The criteria given are commonly used in evaluating patch-test responses, but they are not absolute.

volvement usually together with other areas. Shampoos commonly cause involvement in a rinse-off distribution anterior to and behind the ears, sometimes on the adjacent neck and forehead, and if one shampoos one's own hair, the fingertips may be involved. Hair dye reactions cause severe involvement of the adjacent neck posteriorly, the ears superiorly, and the forehead especially. Beauticians break out on the hands. Allergy to acid perms may cause a similar eruption in the near term and a chronic pattern where the hair touches, since the allergen is retained in the hair. One should also think of dermatitis herpetiformis in the scalp as well as follicular lichen planus, seborrheic dermatitis, seborrheic psoriasis, some types of folliculitis, and pityriasis rubra pilaris. Eruptions limited to the hairy scalp are seldom allergic contact dermatitis.

The Eyelids

Allergic contact dermatitis on the eyelids may occur from nail polish, medications used in the eyes or on the lids, contact lens solution, makeups and the applicator used to apply them, mascara, eyelash curlers, plants, and hand transfer, especially from black rubber, nickel, and so forth. Plant allergens may involve the eyelids, whereas photodermatitis, which can look similar, typically spares that location. In the differential, one must consider atopic dermatitis, seborrheic dermatitis, psoriasis, rosacea, neurodermati-

Table 2
Differential Diagnosis of Contact Dermatitis

Other eczemas
Atopic eczema
Nummular eczema
Stasis eczema
Dyshidrotic eczema (pompholyx)
Asteatoic eczema
Infectious eczema toid dermatitis
Lichen simplex chronicus
ID reactions
Juvenile plantar dermatosis
Frictional lichenoid eruption
Other dermatosis
Cutaneous T-cell lymphoma
Psoriasis
Seborrheic dermatitis
Zinc nutritional and vitamin deficiency
Glucagonoma syndrome
Tinea
Candidiasis
Scabies
Herpes simplex
Lichen planus
Dermatitis herpetiformis
Some bullous dermatosis (Hailey-Hailey, pemphigus, and so on)
Disorders of cornification, and so forth
Graft vs host reactions
Immunodeficiency disease (Wiskott-Aldrich syndrome, and so on)
Phenylketonuria
Drug reactions
Syphilis
Actinic prurigo, polymorphic light eruption, noncontact phototoxicity
Papular urticaria
L.E., dermatomyositis, and so forth
AIDS-related dermatosis

tis, irritant dermatitis, irritation from respiratory allergy, bacterial, herpetic, and fungal infection, and even dermatomyositis.

The Lips and Perioral Skin

Contact dermatitis of the lips includes lipstick dermatitis, caused by any of several ingredients, topical and dental medications, objects habitually chewed, e.g., metal or plastic in pens and pencils, or rubber in pencil erasers, musical instruments, e.g., reeds or wooden instruments (for example, recorders or flutes), flavors, or dental braces (which can also be a source of irritation directly or from drooling). Other conditions to

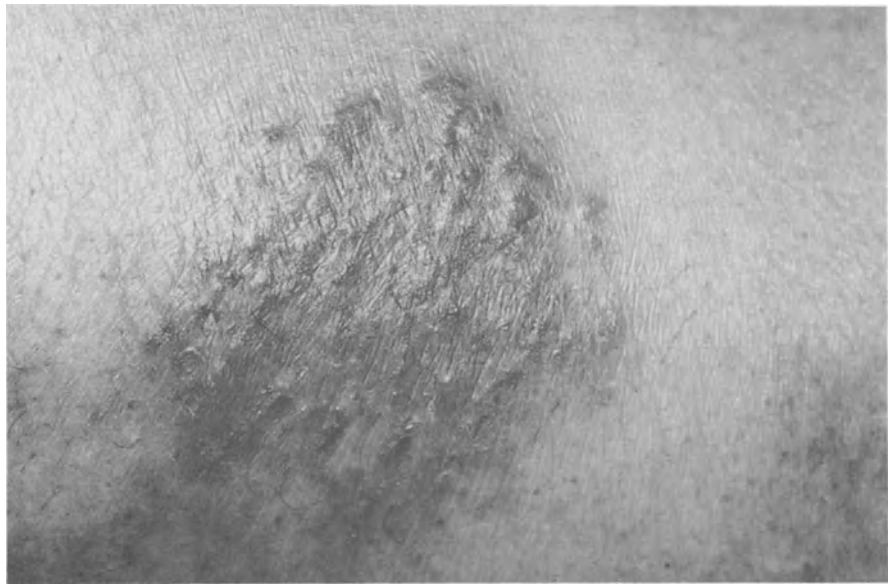

Fig. 10. Coin-shaped plaque of nummular eczema.

be considered include candidal cheilitis, cheilitis glandularis, cheilitis graulomatosis, lichen planus lupus, and actinic cheilitis, to name a few.

In the periorificial locations, contact dermatitis can occur from flavors and other ingredients of orally administered agents, e.g., toothpaste dermatitis at the commisure, hand transfer of black rubber chemicals and metal allergens, e.g., nickel and cobalt, medications used on self and others, and following a visit to the doctor or dentist, rubber dermatitis from the gloves or rubber dam used. One should also think of zinc and vitamin deficiencies as well as glucagonoma. Around the mouth, one can also see an irritant reaction to chronic licking, and lichen planus can localize here.

The Face

On the face, one sees cosmetic sensitivity typically, which may be irritant as well as allergic. However, there are many other causes. Hand transfer occurs from poison ivy and Compositae (weed) allergens, as well as nail polish. Other materials contacted include sources of phototoxic and photoallergic dermatitis, sunscreens, contact with a pillow or a child's favorite doll, and of course, the ubiquitous therapeutic agents, including not only those prescribed, but also the long list of lotions and home remedies so often applied. The list is actually too long to include everything, so one should be circumspect.

The Trunk

On the trunk, clothing dermatitis is often the first thing considered, especially when the eruption is located around the axillae and is worse over the lower rib cage. Causes of

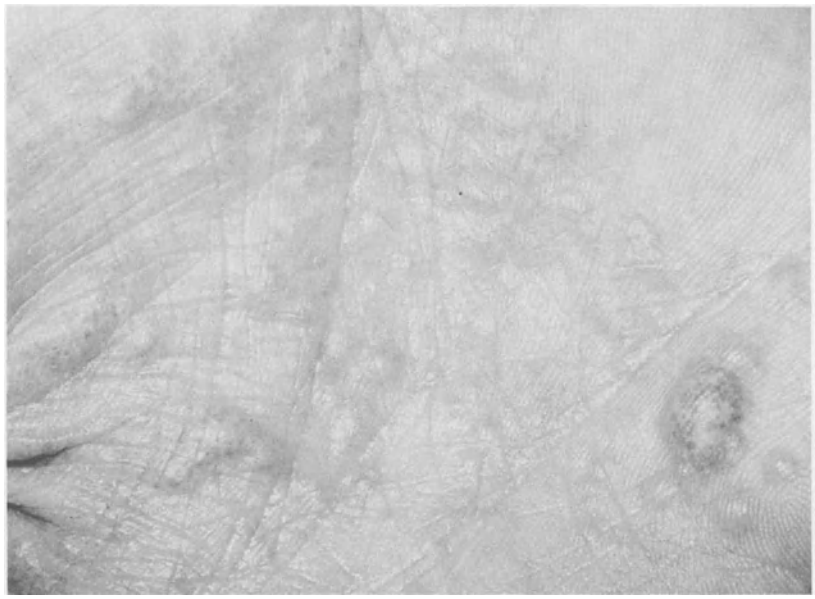

Fig. 11. Dyshidrotic eczema or pompholyx of the palm. Note the deep-seated individual vesicles suggesting an endogenous eczema.

clothing dermatitis include not only formaldehyde-releasing fabric finishes, but disperse dyes, detergents left in clothing (both irritant and allergic), medications used that contaminate clothing, elastic fibers, and even epoxy used to cement pads or to mark labels. Waistband eruptions may be from detergents, or from latex allergens or an antigen in bleached underwear, dibenzyl carbamyl chloride. Other dermatoses found on the trunk include most papulosquamous diseases and cutaneous T-cell lymphoma. Drug eruptions and systemic contact dermatitis can also be a problem here.

The Feet

The feet typically break out to shoes and topically applied materials. The most common pattern of shoe dermatitis is insole dermatitis from either rubber chemicals or adhesive allergens in sponge rubber insoles of athletic shoes. This characteristically involves the plantar surface, except for the proximal toes and the longitudinal arch. The pattern in shoe dermatitis depends on the cause and the points of contact, so one sees a different pattern with leather (chromate) sensitivity and rubber allergy other than the insoles. The differential includes dyshidrotic eczema, atopic dermatitis, id reactions, tinea, psoriasis, lichen planus, cutaneous T-cell lymphoma, and palmo-plantar pustulosis, among other things.

The Lower Extremities

On the legs and thighs, contact dermatitis may be from nickel or phosphorus sesquisulfide in matches, rubber or dyes in stockings, detergents, fabric finishes, cloth-

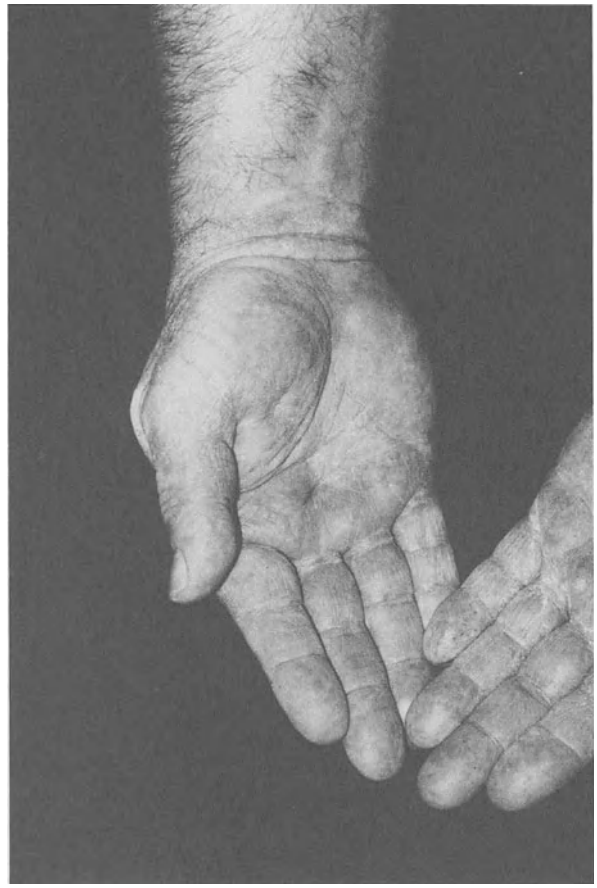

Fig. 12. Hand eczema in a factory worker handling carpet. Reactions on patch testing were from rubber chemicals. The source proved to be rubber backing on the carpet.

ing (Fig. 13), and even reactions from epoxy in knee pads. The differential includes nummular, atopic and stasis eczema (Fig. 14), poison ivy dermatitis (Figs. 3–5), contact from medications (Figs. 8, 9), other eczemas, and many other dermatologic diseases.

EXFOLIATIVE DERMATITIS

Exfoliative erythroderma may be caused by contact and other eczemas (especially atopic dermatitis). However, it may also be caused by malignancy (especially cutaneous T-cell lymphoma), psoriasis, seborrheic dermatitis (especially in infants), pityriasis rubra pilaris, several different congenital ichthyoses, drug eruptions, pemphigus foliaceous, pemphigoid, scabies, and other things. Here a wise generalist will seek consultation early.

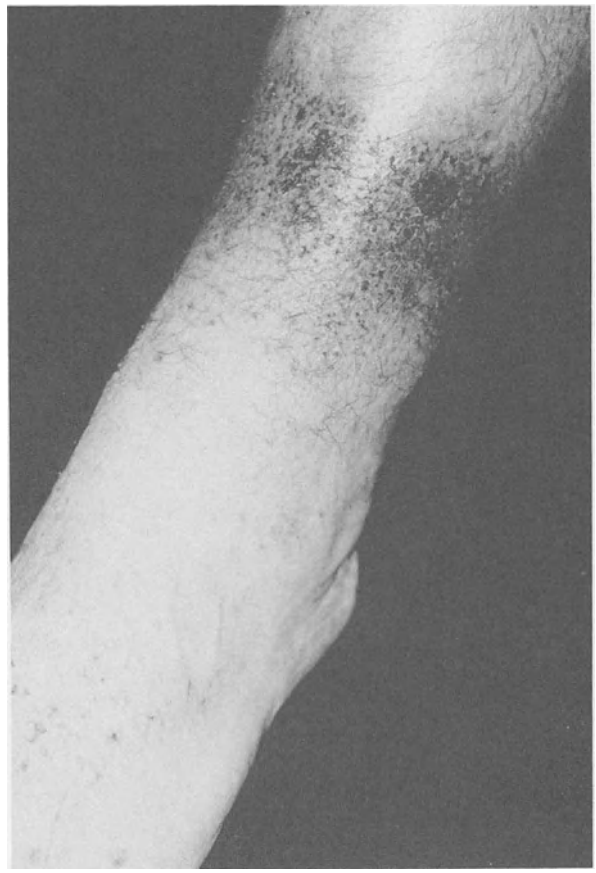

Fig. 13. Allergic reaction to diethylthiourea in a wet suit.

PATCH TESTING

The most important confirmatory test in allergic contact dermatitis (and in establishing a diagnosis of irritant dermatitis) is the patch test. Here one attempts to prove the presence of allergy by reproducing the disease in a controlled situation. Usually standard commercial allergens (Table 3) are used for screening examinations. There are two commercially available sources of patch-test materials in the United States. One set, available from Hermal, contains 20 allergens. The other series, marketed by Glaxo, contains 24 ready-to-use allergens. Both series contain single allergens as well as mixtures. The TRUE test can be applied by removing the cover on each set of 12. These are marked by number with the antigens loaded.

Patch testing is done on clear skin on the upper back. Otherwise aluminum (Finn) chambers on Scanpor tape are usually used to hold the antigens. These are packaged *10/strip with two rows of five.* One should mark the first of these with numbers 1–5 and

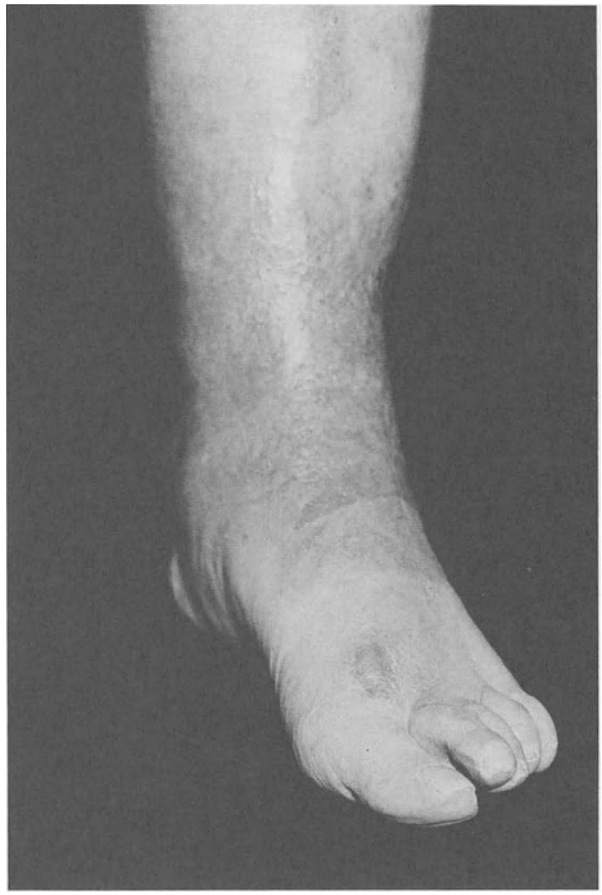

Fig. 14. Stasis dermatitis is often complicated by allergic contact dermatitis to substances applied for treatment or symptomatic relief. This patient was allergic to an OTC lotion.

6–10 along the left and right rows, and the second set of 10 chambers are marked 11–15 and 16–20, prior to removing the cover to load the chambers. The reason for this is that when the cover is removed and the strip is placed on the table for loading, the chambers can easily be turned around. If chambers are not marked, one could easily load the strips backward or even apply them upside down.

The chambers in the TRUE test are already loaded. The Hermal tests are loaded from syringes into the aluminum chambers. Chambers are filled about half to two-thirds full, with liquids loaded last. To hold liquids, one must use a cellulose pad inside a FINN chamber. A dab of petrolatum applied to the aluminum chamber prior to adding the cellulose pad will prevent its falling out. Strips are applied with a rolling motion from below upward, to the upper back while the patient is in a slightly flexed position. The external (upper) arm is an acceptable alternate site, but the forearm is not. The site is marked with a fluorescent highlighter by outlining the paper tape strip and marking each chamber's position on both sides as well as top and bottom. Then the second strip

Table 3
Sources of Standard Contact Allergens

Benzocaine, (caine mix)	H, T	Local anesthetic, OTC preparations, crossreacts with procaine, PABA sunscreen, sulfa, and so on
2-MBT	H, T	Rubber accelerator
Colophony	H, T	Rosin in pine and other conifers; solder flux, tape, mascara, topical and dental medications, varnishes, putty, paint, pine products, and so on; may indicate allergy to fragrance, flavor, chrysanthemum
p-Phenylenediamine	H, T	Permanent hair dyes, may crossreact with black rubber (some), color film developer, sulfa, PABA sunscreens, the benzocaine group, and some epoxy hardeners
Imidazolidinyl urea	H	Preservative found in a variety of cosmetic products
Cinnamic aldehyde	H	Fragrance and flavor ingredient; cinnamon
Wool alcohols	H, T	Sensitizing component in lanolin; found in many cosmetic products and lotions; found in other materials from veterinary products to furniture polish; will not detect all lanolin reactors, so some add Amerchol 101
Carba mix	H, T	Accelerator in rubber products; also found in agricultural chemicals, slimicides, and so on
Neomycin sulfate	H, T	Topical antibiotic; often crossreacts with other aminoglycosides; coreacts with bacitracin
Thiuram mix	H, T	Rubber accelerator especially in latex gloves; closely related to carba mix chemicals; rubber products, agricultural chemicals, animal repellants
Formaldehyde	H, T	In wrinkle-free fabric finishes, cosmetics, shampoo, biocides, paper, plywood, and many other products; released by many preservatives
Ethylenediamine	H, T	In one topical steroid-nystatin generic; May crossreact with Merthiolate, Aminophylline, hydroxyzine
Epoxy	H, T	Resin used in many epoxy adhesives, paints, electrical dielectrics (insulation)
Quaternium-15	H, T	Cosmetic preservative. Releases formaldehyde. In many liquid soaps, shampoos, and other wet products.
p-tert-Butylphenol	H, T	Adhesive in shoes, fiberglass, wood, and so on, formaldehyde resin
Mercapto mix	H, T	Rubber accelerator related to 2-MBT
Black rubber mix	H, T	Antioxidant in (esp. outdoor) rubber
Potassium	H, T	Cement, mortar, leather, inks, paints, dichromate
Balsam of Peru	H, T	Used in the United States to detect fragrance allergy; crossreacts with citrus peel, vanilla, eugenol, colas, flavored beverages
Nickel sulfate	H, T	In steel, jewelry, many metal objects; said not to be available from stainless
Methyl(chloro) isothiazolinone	T	Preservative in wet products, coolant, shampoo, creams, lotions, air conditioners, and so forth
Fragrance mix	T	Mixture of eight perfume chemicals used as screen for fragrance and flavor sensitivity; found as flavors in foods and medications, as perfumes in personal care products from cosmetics, shampoo, and soap to toilet tissue, laundry, and household products
Cobalt	T	Ingredient in metal products, jewelry; commonly coreacts with nickel
Quinoline mix	T	Less frequent reactor; contains iodochlorhydroxyquin or clioquinol (in Vioform) and chlorquinaldol; may also be used in veterinary products
Paraben mix	T	Preservatives in cosmetics, medications, foods, and industrial products
Thimerosal	T	Preservative in contact lens solutions, eye drops, allergy injections, immunization reagents, Tincture of Merthiolate; may predict piroxicam photoreaction; many true positives not relevant

is applied. Remember, the liquids are not loaded until everything else is ready. Chambers are left on 48 h and read at 72 h and once more 1–4 d later. Accurate records, including a diagram, are kept detailing the substances applied, the location of each, the date of application, and the vehicle and concentration used. Since much of this is routine, printed forms can be made up in advance. It helps to include a drawing of the back or the site of application to help identify responses when marks are difficult to locate. It does little good to find a reaction without knowing what caused it.

An important step for those new to the procedure is learning the discipline of reading the tests. This often requires experience. Standard criteria for scoring reactions are as follows: ± reactions show erythema only; 1+ reactions are erythematous, and sometimes raised slightly or with a few papules but not vesicular; 2+ reactions are vesicular; 3+ reactions are bullous and often irritant.

Potential causes of false-positive and false-negative readings are given in Table 4. Once significant (2+ or nonirritant 3+) reactions are found, the relevance must be assessed by comparing the reaction with the probabilities of exposure. The patient should be provided detailed instruction on how to identify sources of that antigen or those antigens. Printed handouts in the patient's language can be found in ref. *1*.

HOW DOES ONE MANAGE A PATIENT WITH SUSPECTED CONTACT DERMATITIS?

The principal rules for complex cases of suspected contact dermatitis involve the following procedure:

1. Remove the patient from all possible contact sources in the involved area. Of course, some situations are difficult; e.g., in clothing dermatitis, one cannot go without clothing. However, all white, polyester textiles are seldom a problem, and such materials are a good substitute. Many women are reluctant to omit wearing makeup, but they are much more receptive when shown the potential for developing additional allergy (meaning they will have difficulty eventually finding products they will tolerate) if not removed from a source of allergic contact dermatitis.
2. Patch test the patient to lotions he or she has applied and to cosmetic materials used on the site, provided they are known to be nonirritant. One can usually test to a moisturizer lotion by placing it in an aluminum patch-test chamber using the cellulose pad. One should **not** test to mascara, cleansing cream, soap, shampoo, and so on, since these are irritant. A cavalier willingness to apply unknown and often irritant materials, especially from work, can cause deep ulcers, scarring, and can even sensitize the patient.
3. Avoid all products giving a positive test and all products possibly containing a chemical giving a positive test.
4. Reinstitute products giving a negative test one at a time.
5. Treat with a steroid in petrolatum (only), and test to this to be sure it is tolerated. Hydrocortisone has to be tested as an intradermal (1 mg SoluCortef/0.05–0.1 mL) and read at 72 h. Any erythema at that time is suspect, and most can be confirmed with a usage test to one area.

   Application to the face should be done without touching the area with the hands. A vinyl glove or a finger wrapped in Saran Wrap™ can be used to apply the steroid ointment. This avoids hand transfer.

Table 4
Potential Causes of False-Positive and False-Negative Reactions to Patch Testing for Contact Dermatitis

False-positive reactions
Nonspecific (irritant) responses
Inappropriate solvents, acids, alkalis, and so on
Irritant interaction of aluminum chamber with metal antigens
Nonspecific pustular responses to metals
Concentration, evaporation of liquid, edge effect
Unknown materials
Contamination
Concentration errors
An "angry" back (skin responds nonspecifically to multiple stimuli)
Mislabeling
Misreading
Allergy to test apparatus (tape, chambers, and so on)
Color left by colored allergens
Phototoxic reactions
False-negative reactions
Technical failure
Separation of patch from skin (inadequate occlusion time)
Loss of occlusion
Time of reading (too early or too late)
Material not fresh
Improper marking
Only one reading done (*see text*)
Failure to employ light in photodermatitis reactions
Patient taking systemic corticosteroids or applying topical corticosteroids at site of application
Inadequate penetration
Wrong site used to apply patch
Test applied to hairy skin
Inadequate dose of allergen
Time of application too brief

6. Finally, the solution to managing allergic contact dermatitis is to avoid contact with all offending agents. In addition, and especially for hand eczema, the patient must be taught how to perform normal daily functions without irritation, since the inflamed skin is **very** easily irritated, which will prolong the time to recovery.

MANAGEMENT

The most important aspect of the management of chronic contact dermatitis is identification of the causative agent. Subsequent to identification, of course, the treatment is avoidance. Patients with chronic contact dermatitis cannot, of course, be treated with systemic corticosteroids, and topical corticosteroids do not, in themselves, remedy the situation. Thus, identification of the causative agent as noted above, and removal of this agent, is the therapy of choice.

For acute contact dermatitis, such as poison ivy dermatitis, patients can be safely treated with short courses of oral corticosteroids. For example, prednisone, given in an initial dose of 60 mg daily, and tapered over a 10 to 14 d period, is sufficient to suppress symptoms in almost every instance.

Adjunctive measures for acute cases could be cool tap water applied as a soak or compress, and mild cases, not requiring oral corticosteroids, can be treated by the application of hydrocortisone cream. OTC agents can suffice in the mildest of cases.

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15 Food Allergy and Intolerance

John A. Anderson, MD

CONTENTS

INTRODUCTION

Definitions and Classifications

Adverse reactions to foods can be divided into two major groups: food allergy, which depicts an immunologic, usually involving IgE, reaction to a food, and food intolerance, which involves all other adverse reactions, some of which are the result of unknown mechanisms, but none of which involve immune reactions (*see* Table 1). Food anaphylaxis is an IgE-mediated, generalized, clinical reaction to a food because of mast cell/basophil chemical mediator release after first sensitization and then re-exposure to the same food. Anaphylactoid reactions to a food or food additive clinically resemble food anaphylaxis, but do not involve IgE sensitization and are the results of direct chemical mediator release from the mast cell/basophil.

Other terms that are occasionally used to describe types of food intolerance include food toxicity or food poisoning, idiosyncratic reactions, and pharmacologic reactions to foods. *Food toxicity* may be the result of natural or acquired toxins in some foods, or the result of microorganisms or parasitic contamination of natural or processed foods. Some of these clinical reactions are "allergic-like" and must be differentiated from food allergy. An idiosyncratic reaction to a food also resembles allergy, but does not involve immune mechanisms. Primary and secondary lactose sugar intolerance, because of the lack of bowel wall enzyme lactase to digest the sugar, is an example of such a reaction. Finally, a pharmacologic reaction occurs to some foods containing chemicals (e.g., caffeine), and some food additives (e.g., food colors) have drug-like effects.

From: *Allergic Diseases: Diagnosis and Treatment*
Edited by P. Lieberman and J. Anderson Humana Press Inc., Totowa, NJ

Table 1
Classification of Adverse Reactions to Foods

Food allergy (immunologic reaction)	Food anaphylaxis and urticaria/angioedema (IgE-mediated)
	Other immunologic reactions to foods
Food intolerance (nonimmunologic reaction)	Anaphylactoid reactions to foods or food additives
	Food toxicity or poisoning (usually owing to contamination)
	Idiosyncratic reaction to a food (e.g., enzyme deficiency)
	Pharmacologic reaction to a food (drug-like effect)

Incidence and Prevalence

The incidence of food intolerance reactions greatly exceeds food allergies in all age groups. Only some food intolerance reactions resemble allergic reactions. One well-documented study of 480 consecutively born infants found that the prevalence of adverse reactions to foods confirmed by double-blind, placebo-controlled food challenge (DBPCFC) during the first 3 yr of life was 8%. In three well-done studies involving infants (United States, Sweden, Denmark), the prevalence of allergic and intolerance reactions to cow's milk protein was found to be 2%. One study, based on the prevalence of documented food additive reactions among 4274 Danish schoolchildren, found the incidence of such reactions in children in general to be 1–2%.

In a single study involving the prevalence of serious anaphylaxis and anaphylactoid reactions seen in 73 emergency departments in the state of Colorado over a 2-yr period (ages 2–71), it was estimated that the overall incidence of such reactions that occur yearly in the United States is 0.004% or 1:250,000 population. Other well-documented studies among adults regarding the incidence or prevalence of allergic and allergic-like food/food additive reactions have not been done, but it is estimated that such reactions in adults are much less than in infants and young children, and range between 1 and 2% of the population.

Natural History of Clinical Reactions to Food Allergy

Among children in whom allergic and allergic-like food reactions have been documented by DBPCFC during infancy, 80–87% were able to tolerate that food on rechallenge by 3 yr of age. The usual foods to which these children were clinically sensitive for originally were cow's milk, eggs, wheat, or soy proteins. In general, the more severe the original reaction to the food, the longer it takes for clinical tolerance to be achieved.

In studies among children and adults who have had documented anaphylaxis to peanuts, the susceptibility to anaphylax on re-exposure lasted at least 14 yr. On the basis of this study and numerous case reports, peanut allergy as well as allergy to other foods commonly associated with systemic anaphylactic type of generalized reactions, such as crustacean seafood (shrimp, lobster, crab, crayfish), fish, tree nuts (walnut, pecan, almond, Brazil nut, filberts, cashews), and seeds, are lifelong sensitivities (*see* Tables 2 and 3).

Table 2
Clinical Reactions to Food and Food Additives

Anaphylaxis	General reactions
	Isolated reactions to the skin (e.g., urticaria with and without angioedema)
	Systemic reactions (laryngeal edema, rhinitis/conjunctivitis, asthma, shock, death)
	OAS
	F-EIA
Atopic dermatitis exacerbated by food allergy	
Gastrointestinal reaction (involving food)	Infant formula allergy or intolerance and enterocolitis/colitis
	Vomiting, diarrhea, and blood loss
	Eosinophilic gastroenteritis
	Celiac disease
Pulmonary reaction (involving food)	Heiner's syndrome
	Rhinitis and asthma
Other food-intolerance reactions that may be confused with allergy	Food poisoning and toxicity (including anaphylactoid reactions to histamine-containing foods)
	Primary and secondary lactose intolerance
	Migraine and other headaches
	Vasoactive amines
	Specific food-induced mediator release
	Reactions to specific food additives
	Chinese Restaurant Syndrome owning to MSG
	Asthma owing to SO_2/sulfites
	Urticaria owing to colors and possibly other agents (sodium benzoates, BHA, BHT, nitrates)
	Behavioral effects
	Sugar
	Color in ADD
	Pseudo-food allergy

Table 3
Usual Foods and Food Additives Associated with Adverse Reactions

Condition	*Likely causative food or additive*
Anaphylaxis (generalized systemic and urticaria/angioedema)	Egg and cow's milk (children); peanuts; tree nuts (almond, Brazil nut, cashew, filbert, pecan, walnut), crustacean seafood (shrimp, lobster, crab, crayfish), fish, seeds
Oral Allergy Syndrome	Pollen sensitivity — Raw food Ragweed — Melons (watermelon, cantaloupe), bananas Birch tree — Apple, pear, hazel nut, carrot, potato, celery, kiwi Grass — Peaches, celery Mugwort — Celery
F-EIA	(Within 2 h) any meal, or celery, shrimp, oyster, chicken, peach, wheat
Infantile atopic dermatitis	Egg, cow's milk, peanut, wheat, soy
Infantile formula intolerance	Conventional cow's milk- or soy protein-based infant formula
Celiac disease	Gluten: wheat, oat, rye, barley
Heiner's syndrome	Cow's milk protein
Scromboid fish poisoning	Tuna, mackerel, bonita, mahi mahi, bluefish
Urticaria from histamine-containing or releasing foods	Histamine-containing foods Parmesan and Roquefort cheese, spinach, eggplant, wines Histamine-releasing foods Chinese restaurant foods, alcoholic beverages (especially red wine), strawberries, seafood
Lactose intolerance	Lactose sugar in cow's milk, cheese, yogurt
Headaches (especially migraine)	Vasoactive amine — Food Caffeine — Coffee, cola Phenylethylamine — Cheeses (especially Gouda and Stilton) Serotonin — Banana, pineapple, plantain, avocado, plum, tomato Theobromine — Chocolate Tyramine — Camembert and cheddar cheese, yeast, red wine, pickled herring, chicken livers
Chinese Restaurant Syndrome	MSG
Asthma owing to a preservative	SO_2, sulfites, yellow color (uncommon), MSG (rare, if any)
Urticaria owing to a food additive	Colors, especially yellow, red, blue (BHA, BHT, sodium benzoate, nitrites—rare, if any)
Attention Deficit Syndrome	Colors, especially yellow

In individuals who are allergic to pollens, usually with allergic rhinitis and conjunctivitis, some are also allergic to fresh fruits and vegetables. This tendency owing to a crossreactivity (e.g., ragweed pollen and melons plus bananas) (*see* Table 3). Although the natural history of this association is not entirely clear, it appears that this type of food sensitivity correlates with the degree of clinical reactivity to pollens.

MECHANISMS OF ALLERGIC AND ALLERGIC-LIKE INTOLERANCE REACTIONS TO FOODS AND FOOD ADDITIVES

Food Allergy

Almost all cases of allergic reactions to foods are the result of Type I immune reaction involving IgE antibody directed to that food. As with other allergic reactions, the susceptible person must be first exposed to the food protein, usually intermittently over a period of time, before sensitization occurs. This process involves the development of IgE antibody to that specific food protein.

Once the IgE antibodies are formed, they tend to stick to tissue mast cells on the surface of the body and, in some cases, circulating basophils. The mast cells and the basophils are the effector cells of allergy and contain either preformed chemical mediators or are able to facilitate formation of other mediators in the immediate tissue around the cell once stimulated (*see* Chapter 5). Re-exposure to the same food protein results in chemical mediator release or formation in the tissue, which causes the clinical allergy signs and symptoms.

The major food allergens are heat-stable. Thus, individuals who are allergic to such foods as milk, peanut, or fish, can develop symptoms once sensitized to exposure to very small amounts of these foods in a natural, cooked, or processed form. There are also minor food allergens, such as those in fresh fruits and vegetables, that crossreact with pollens in the oral allergy syndrome. These allergens are heat-liable. Individuals allergic to a fresh fruit, such as apple, can usually eat an apple pie. A recent study would seem to indicate that a short microwave exposure to a fresh fruit is enough to denature the allergen to allow it to be tolerated by individuals who develop symptoms to these fresh fruits.

Although there is some immunologic crossreactivity between different foods, especially those in the same food family, characteristically, individuals react clinically more often only to a few foods in a given food family. For example, in the legume family, most individuals are clinically sensitive only to peanut and can tolerate peas, beans, and soy protein, even though IgE antibodies to these foods can be detected either in IgE immediate reacting skin tests or in vitro IgE food protein-specific antibody assays.

Exposure to food protein usually occurs orally. Occasionally, individuals can become sensitized or, after developing a food allergy, have a reaction to re-exposure of food through either the aerosol or contact route. Examples include bakery workers who develop IgE-mediated wheat protein sensitivity (and subsequent asthma called baker's asthma) from exposure and then re-exposure to wheat flour dust. Another example is the fish-allergic individual who may develop urticaria or systemic anaphylaxis when exposed to odor/steam of cooked fish.

In food-dependent exercise-induced anaphylaxis (F-EIA) (*see* Table 2), increased histamine release is induced by exercise. IgE reactions to foods only become clinically evident within 2 h of a meal, followed by vigorous activity. Atopic dermatitis is a skin condition, primarily in children, whose pathogenesis involves both nonimmune and immune factors. IgE antibody formation in general is usually enhanced in this condition. However, in only one-third of children with atopic dermatitis is food allergy clinically important.

It has been shown in studies with atopic dermatitis individuals who are proven to be allergic to a food by DBPCFC that, while eating that food, in vitro histamine release is increased non specifically owing to the presence of "IgE-dependent histamine-releasing factors" in the serum. This tendency has a definite connection with the broad-based chronic inflammation found in the skin of the atopic dermatitis patient who is allergic to specific food proteins. The IgE reaction that results in the eczema type of rash in atopic dermatitis may be an example of a late-phase IgE reaction.

Another type of immunologic reaction to food is a rare syndrome called the "Heiner's syndrome" (*see* Table 2). In this syndrome, infants develop high IgG antibody titers to cow's milk through aspiration and sequestration of the milk protein in the lung. Subsequently, on repeated oral milk exposure, pulmonary infiltrates result. This reaction is believed primarily to be owing to a Type III immune reaction resulting from IgG milk antigen–antibody complexes with activation of complement. There is some evidence for a Type IV cell-mediated immune reaction owing to this cow's milk protein. In celiac syndrome, the pathogenesis points toward both a toxic reaction to wheat gluten and a Type IV cell-mediated immune reaction to this wheat protein.

Allergic-Like Food Intolerance Reactions

The mechanisms for most food intolerance reactions are not known. Most infants who develop isolated GI symptoms (vomiting, diarrhea, blood in stool) resulting from formula intolerance do not demonstrate IgE antibody reactions. This condition can occur while the child is ingesting cow's milk-based conventional formula, breast milk from mothers eating a normal diet, or soy protein-based infant formulas. Approximately one-half of the case reports of individuals with documented eosinophilic gastroenteritis are allergic. The rest are not, yet the disease pathology between the allergic and non-allergic group is similar.

An example of an anaphylactoid reaction to food is a "scromboid fish poisoning" (*see* Tables 2 and 3). In this situation, certain fish are spoiled or contaminated with either proteus or *Klebsiella* species of bacteria, such as tuna, mackerel, bonito (scromboid varieties), or mahi and bluefish. The bacteria decarboxylate histadine in fish tissue to create histamine. When the fish is cooked and eaten, the diner experiences a sharp peppery taste, burning of the mouth parts, followed by nausea, vomiting, diarrhea, facial flush, and headache—all resulting from the high levels of histamine in the tissue. This is the same major chemical mediator released from the mast cell or basophil as the result of an allergic reaction.

Other common foods that may contain a significant amount of histamine include Parmesan and Roquefort cheeses, spinach, eggplant, red wines, and some Chinese restaurant foods (*see* Table 3). Other pharmacoactive agents in foods that may produce

symptoms that could be confused with allergy include caffeine (in coffee and cola), tyramine (in cheese), phenylethyline (in cheese, red wine, and chocolate), serotonin (in banana, pineapple, avocado, tomato), and theobromine (in chocolate) (*see* Table 3).

The possible effects of these various natural vasoactive amines are variable, but there are reports of these chemicals aggravating migraine headaches. Patients on monoamine oxidase (MAO) inhibitor drugs for the treatment of such conditions as depression need to be very careful about eating these types of foods, since MAO is important for the metabolism of vasoactive amines. Thus, when eating these foods and on these inhibitor drugs, increased blood levels of the vasoactive amines may result. Both severe blood pressure elevation and headache have been reported.

Lactose intolerance is an idiosyncratic reaction caused by the lack of bowel wall lactase, which is necessary to metabolize lactose sugar found in cow's milk. Individuals with lactose intolerance who ingest milk cannot digest it, and the sugar ferments in the bowel, causing gas, discomfort, and perhaps diarrhea. Primary lactose intolerance is a common inborn error of metabolism in certain population groups (e.g., approx 80% of North American African-Americans, Arab, and Asian populations). This condition is a less common problem in other ethnic groups (10% incidence in North European Caucasian populations).

The symptoms begin about age 7, but may occur earlier if the patient develops a severe viral or bacterial gastrointestinal infection. Lactose intolerance may occur after any GI infection and is usually a temporary condition lasting about 2 wks. Secondary lactose intolerance of a more permanent nature, however, can occur with chronic gastrointestinal conditions, such as Sprue or cow's milk allergy. Each patient with lactose intolerance is different, and many may tolerate some degree of lactose sugar in their diet.

Food Additive Intolerance Reactions

Allergic reactions have been reported to occur to the preservative sulfites (and SO_2), sodium benzoate, butylated hydroxyzole (BHA), and butylated hydroxytyluene (BHT), the sugar substitute aspartame, artificial colors (especially yellow, red, and blue), and the flavor enhancer monosodium glutamate (MSG). The symptoms of principal concern are urticaria and asthma. In most cases, even if it is proven that the food additive is involved in the clinical symptoms, the exact mechanism of the reaction is unknown.

In sulfite-induced asthma, the principal mechanism is believed to be the inhalation of SO_2 as sulfite-containing foods are chewed in the mouth. In addition, a small number of individuals have been identified who have a sulfite oxidase enzyme deficiency, which prevents metabolism of this preservative and could result in high blood levels. In a few cases of documented urticarial reactions to color, histamine and prostaglandin elevation has been found in the urine after specific food allergy additive challenge. In the attention deficit syndrome with hyperactivity (ADD), food colors, especially yellow, have been implicated in 3% or less of the cases in inducing a "drug-like" effect on the patient's ability to learn.

The evidence for IgE-mediated food immune reactions as being involved in the pathogenesis of migraine headaches is very poor. However, there are a small number of documented cases of migraineurs who, on DBPCFC, demonstrate increases in plasma

histamine PGFα and PGD_2, that correlate with specific food protein challenge and headache.

CLINICAL REACTIONS TO FOODS AND FOOD ADDITIVES (*SEE* TABLE 2)

Food Anaphylaxis

The signs and symptoms of anaphylaxis resulting from food allergy are no different than those owing to anaphylaxis as the result of allergy to β-lactam antibiotics, stinging insects, or natural rubber latex (*see* Chapter 5). The symptoms and signs may be mild or severe. Milder symptoms/signs include contact urticaria, generalized pruritus, erythema, and urticaria with or without angioedema. More severe symptoms occur with generalized systemic anaphylaxis owing to a food and may be multiple or single in nature. These symptoms include laryngeal edema, rhinitis with or without conjunctivitis, asthma, blood pressure decrease or shock, and possible cardiovascular collapse and death. Occasionally, additional symptoms include nausea, vomiting, abdominal cramps, diarrhea, and uterine or bladder cramps.

Most generalized anaphylactic reactions to foods of any significance are biphasic in nature with an early and late phase separated by about 1–8 h. Some very serious reactions are protracted, and last continuously for 5–32 h without remission. Individuals tend to develop serious anaphylactic reactions to a relatively small group of foods, including cow's milk and eggs (usually infants and children), peanuts, tree nuts (walnut, pecan, almond, cashew, Brazil, filbert), crustacean seafood (shrimp, lobster, crayfish), fish, and seeds. (*see* Table 3).

Most individuals who die or nearly die with food anaphylaxis are very allergic in general and reactive to many things in their environment, including pollen, animals, house dust, and mold allergens. Most of these patients have allergic rhinitis and asthma. Individuals who have been reported either to have died from or nearly died from a systemic reaction from food are aware of their specific food allergy. Most deaths occur when the individual is away from home. The specific food to which the individual is allergic is usually eaten in a disguised form (e.g., in a pastry, candy, salad, sandwich, or hors d'oeuvre). Often the difference between life and death is whether or not adrenaline is given quickly (e.g., within 1 h after the start of a reaction) when the dangerous food is ingested or the exposure occurs.

There are two special anaphylaxis syndromes that are specific for food allergy. The first is called the oral allergy syndrome (OAS) or the fruit and vegetable syndrome (*see* Table 2). In this syndrome, individuals with pollen sensitivity, usually manifested by allergic rhinitis/conjunctivitis or hay fever, develop specific food sensitivities to fresh fruits and vegetables on contact of these raw foods with the mouth. The mechanism is owing partly to a crossreactivity between the pollen protein and the food protein (*see* Mechanisms). The food cross reactivities include melons and bananas among US ragweed-allergic individuals; apples, pears, potatoes, hazelnuts, carrots, celery, and kiwi among birch pollen-allergic individuals; peach, tomato, and celery among grass allergic individuals; and celery allergy among European mugwort weed-sensitive individuals (*see* Table 3). These crossreactivities between foods and pollens may be further

Proven Food Allergy in Infants

The most likely foods involved in allergic reactions in children below the age of 2 in the United States are

- Cow's milk
- Eggs
- Peanuts
- Wheat
- Soy

Food Anaphylaxis

Lifelong sensitivity may occur at any age to these commonly eaten foods:

- Peanuts
- Seafoods (especially shrimp, lobster, and crab)
- Tree nuts (e.g., almonds, Brazil nuts, cashews, filberts, and pecans)
- Fish
- Seeds

complicated by the fact that individuals with anaphylaxis to natural rubber latex may also be sensitive to certain foods, including bananas, chestnut, avocado, and kiwi, and that these sensitivities may be owing to crossreactivity between pollens, such as ragweed and grass.

The symptoms of OAS are usually confined to exposure to the raw foods to either the mouth or hand, and the type of symptoms include pruritus, swelling, tingling, or fullness. In some cases, full-blown systemic anaphylaxis may result. In the majority of cases, however, symptoms begin within 5 min of raw food contact, and may be ameliorated by discontinuing contact and washing the hands or rinsing the mouth so that symptoms resolve within 30 mins.

A second food-specific anaphylactic syndrome is food-related exercise-induced anaphylaxis (F-EIA). EIA is a relatively newly described physical urticaria in which vigorous exercise is associated with urticaria or shock. In half the cases, this syndrome requires a cofactor, such as eating a meal (in general) or ingestion of a specific food, including celery, shrimp, oysters, chicken, peaches, or wheat (*see* Table 3). All symptoms begin within 2 h of a meal and usually the individual can eat the specific food in spite of the presence of IgE antibodies to that food, as long as he or she does not exercise in this 2-h period.

Atopic Dermatitis

Although atopic dermatitis is a primary skin disorder of children, in approx 80% of the cases children are allergic in general and have high total IgE and many positive skin

test reactions or evidence of in vitro antiallergic antibodies. Some of these reactivities are directed to foods. It has been proven, using DBPCFC, that about one-third of children with atopic dermatitis react with an exacerbation of their rash to specific food challenge, such as eggs, cow's milk, peanut, wheat, and soy (*see* Table 3). Other clinical reactions to foods in this group of patients are less common. It has been found in studies using DBPCFC involving food allergic atopic dermatitis children that the allergy skin test or in vitro test is usually positive to the offending food, but that the likelihood of that food being clinically significant in the rash is no more than 50%.

In these studies, if the food skin test was negative, the DBPCFC was almost always also negative. It was found in these studies that the skin test and in vitro IgE food antibody test results were more reliable as an index of possible food involvement than was the mother's history of such reactions. Individuals who were found allergic were usually sensitive only to a few foods, not multiple foods. A negative food skin test or in vitro IgE food antibody test practically ruled out the possibility that the DBPCFC would be positive to that food. It has also been shown that if the food to which the patient was found to be allergic on DBPCFC was eliminated from the diet for a period of time, the dermatitis in general would improve (*see* Mechanisms).

Gastrointestinal Reactions Involving Food

A wide variety of signs and symptoms involving the gastrointestinal tract could be attributed to a food allergy. However, most are not specific, and the possible causes for most of these signs and symptoms are multiple. Itching and swelling of the mouth, however, are certainly suggestive of an allergic reaction as in the OAS. Infants who have formula intolerance can develop vomiting, have diarrhea, or simply have blood loss in the stool. Some individuals simply fail to thrive.

In food-induced enterocolitis, both the small and large bowel are usually involved. The bowel wall of the small intestine, in particular, is infiltrated with lymphocytes, plasma cells, and eosinophils. Formula (usually cow's milk protein)-induced colitis resembles ulcerative colitis, and is characterized by friable mucosal surfaces, eosinophilic infiltrates, and either occult or gross blood loss. In these infants, often the elimination of conventional cow's milk-based infant formula feeding and replacement with a casein hydrolysate infant formula, plus rechallenge to conventional formula, is the only way to prove the etiology, since IgE antibodies to the food protein may not be found in in vitro studies.

Eosinophilic gastroenteritis is a chronic problem of older children and adults that involves the entire GI tract (especially stomach and small intestine). These tissues are infiltrated with eosinophils. The symptoms include cramping, abdominal pain, nausea, vomiting, diarrhea, and blood loss in the stool. Only one-half of the reported cases of eosinophilic gastroenteritis are highly allergic, including reactions to many foods. When these specific foods are eaten, the condition is exacerbated. When the patient switches to a diet devoid of offending foods, however, the condition does not completely clear.

Celiac syndrome is less commonly diagnosed now than previously. The primary cause is gluten, usually from wheat protein (*see* Table 3). The classic, full-blown picture of the once thriving infant who becomes wasted, has an obvious protracted abdomen,

and suffers from chronic diarrhea and rickets is now not generally seen. When this condition is diagnosed currently, it is usually in a child with growth retardation and anemia, or in an adult with chronic weight loss and persistent diarrhea.

Infant colic is not the result of food allergy. It occurs in 20% of children, regardless of the diet, including maternal breast milk. Recurrent abdominal pain in older children usually has nothing to do with food allergy. Intermittent bouts of diarrhea, along with abdominal cramping, are again not likely to be owing to food allergy. Probably the most common problem diagnosed under these circumstances is an irritable bowel syndrome. However, other conditions, such as ulcerative colitis and regional ileitis, polypoid disease, and cancer, must be ruled out.

Pulmonary Reactions Involving Food

In 1956, D. Heiner and his colleague J. Sears diagnosed a group of infants with recurrent anemia and pneumonia associated with in vitro cow's milk precipitins in the serum. Some of these children later developed pulmonary hemosiderosis. This syndrome is believed to be the result of pulmonary aspiration of milk formula just after birth and the development of IgG cow's milk antibody titers owing to sequestration of milk in the lung (*see* Mechanisms). Later, on repeated exposure to cow's milk in the diet, both a Type III immune complex and a Type IV cell-mediated reaction occur. Today, such reactions in infants are rare, but should be considered in infants with recurrent pneumonia and anemia of undetermined etiology.

Rhinitis and/or asthma-like symptoms (wheezing, respiratory distress) occur as part of systemic anaphylaxis to foods. It has been shown in studies of children with atopic dermatitis who are allergic to foods that after specific food avoidance, followed by DBPCFC 2 wks later, one-third are likely, on challenge, to develop respiratory symptoms, such as rhinitis or asthma, along with their exacerbation of skin rash. Other than this situation, rhinitis and asthma are unlikely to be triggered by food. This is particularly true of adults or older children with these conditions.

Other Food Intolerance Reactions That May Be Confused with Allergy

Reactions, such as anaphylactoid events following scromboid fish protein, are described under Mechanisms to the foods listed in Table 3. Urticaria may occasionally occur following ingestion of certain foods containing histamine or as histamine reactors as listed in Table 3. Examples include cheese, red wine, or strawberries.

One of the most common gastrointestinal problems that is confused with milk allergy is primary (and secondary) lactose intolerance. The mechanism of this reaction is described under Mechanisms. As pointed out, the problem with milk usually begins around age 7 among North American African-Americans, but may start earlier in childhood if the child has had a significant gastroenteritis. Then, for the rest of his or her life, milk is a problem. This sequence of events is different from the individual who is milk-protein-allergic in that the milk-allergic individual has trouble during early childhood and later is able to tolerate milk clinically.

In the lactose-intolerant patient, the degree of exposure to milk sugar is important. Certain foods are better tolerated than others in that cheese is better tolerated than whole milk and naturally fermented yogurt is better tolerated than cheese. Since the problem is

Food Additive Reactions

- In general, proven adverse reactions to food preservatives, colors, or flavor enhancers are uncommon.
- Chewing foods containing sulfites may release SO_2, which, when inhaled, may exacerbate asthma.
- Very few patients have been proven to develop urticaria after ingesting food coloring agents.
- Behavioral abnormalities in children usually cannot be attributed to diet content (e.g., amount of sugar, presence of allergic protein, or type of food additive).

common in certain ethnic groups, older family members may report the same problem with milk ingestion, and lactose intolerance is usually simple to diagnose. If it is important to document this syndrome, this can either be done by a gastroenterologist using a breath hydrogen test or a lactose tolerance test.

The triggering of headaches by vasoactive amines naturally or by food additives may occur with the foods listed in Table 3 and described under Mechanisms. Although the issue of allergy being involved in migraine headache pathogenesis has been long debated, it is rarely proven. In a few cases of patients with migraine headaches, chemical mediator release while eating a specific food may be involved in the headache. Migraines are very common in the general population (e.g., 25% of all adult women and 15% of all adult men). In addition, allergies are also common (20% of the population in general). Therefore, it would be usual to see both conditions (migraine headache and atopic disease) present in the same individual.

Adverse reactions to food additives are not nearly as common as generally believed. Reactions to BHA, BHT, benzoates, and nitrates are very rarely substantiated by objective measurements. The most common FDA reported food additive reactions are those resulting from aspartame, and the usual type of symptom is headache. Fifteen percent of reports of adverse effects owing to aspartame, however, are "allergic-like," usually urticaria. Although there are two documented cases of aspartame-induced urticaria/angioedema reported in the world literature, a recent large nationwide, multicenter study using DBPCFC was unable to confirm a significant association between aspartame and urticaria. The types of adverse reactions to food additives that have been confirmed over the years include the Chinese restaurant syndrome resulting from MSG, asthma resulting from SO_2 or sulfites in food, and occasional episodes of urticaria/angioedema resulting from food coloring (*see* Tables 2 and 3).

The first report of the Chinese Restaurant Syndrome was a self-report of a Chinese physician in 1968 who ate at a Chinese restaurant and experienced symptoms of nausea, headache, sweating, thirst, facial flushing, tightness and burning of the face and chest, abdominal pain, tearing of the eyes, and a sensation of "crawling" in the skin. Typically, the symptoms begin 15–30 min after eating a meal containing a large amount of MSG, which is a salt of a glutamic acid. These symptoms usually subside without specific medical treatment once the individual discontinues ingestion of the MSG-containing food.

The food additives that are the second most likely (after aspartame) to be reported to the FDA as being responsible for adverse reactions are sulfites and SO_2. Although a few cases of anaphylactoid type of reactions, usually involving urticaria/angioedema, have been reported, most reactions are the result of asthma exacerbation in a known asthmatic. Some of the early cases were serious and a few led to death. Although SO_2 and sulfites have been used for many years as food and beverage preservatives, it was not until the 1970 to 1980s that reports emerged about serious asthma attacks being precipitated directly on opening a package containing SO_2-preserved foods or eating (and inhaling SO_2 indirectly) sulfite-containing foods (*see* Mechanisms). Of particular importance were fresh vegetables and fruits in salad bars in restaurants (especially lettuce) to which a sulfite solution had been applied to preserve that food. The FDA has estimated that approx 5% of all asthmatics are at risk for a reaction to SO_2 or sulfite, and studies have shown that the more serious asthmatic is at greater risk of an exacerbation of his or her asthma than a mild asthmatic.

In the late 1980s, the FDA made significant changes in the regulations concerning the maximum level of sulfites that could be in processed in foods in the United States, as well as restrictions on the use of sulfites in restaurants, especially in salad bars. Since that time, the number of reports of sulfite-induced asthma has dropped dramatically. Although there have been reports of MSG-induced asthma exacerbations (in Chinese restaurants in Australia) that were confirmed by challenge studies in the 1980s, there has not been a similar problem with MSG in the United States.

Although in Europe food additives of all types have been implicated as primary causes of chronic urticaria in about 15% of the cases, studies in the United States have failed to confirm a significant relationship with any additive except for a few isolated cases of color (particularly yellow)-induced urticaria and angioedema (*see* Table 3). Tartrazine (FD&C yellow #5) was originally believed to "crossreact" in some way with aspirin and to be a factor among asthma exacerbation in ASA-sensitive individuals. Careful DBPCFC with tartrazine in proven aspirin-sensitive asthmatics have failed to confirm this association with yellow #5. Independent of aspirin sensitivity, there are a few isolated asthmatic patients who are sensitive to yellow #5.

Food additives (particularly colors, especially yellows) have been implicated in causing or exacerbating behavioral problems in children. Probably the most widely known theory regarding this relationship was the Feingold theory about colors (and other food additives) causing hyperactivity in patients the attention deficit disorder (ADD) (*see* Tables 2 and 3). Most subsequent studies have shown that colors do have a drug-like effect, but that this effect occurs in no more than 5% of children with ADD and the effect has to do with learning abilities. There are no studies that show that colors in the market today are not safe for the general population.

In the mid to late 1980s, diets high in sugar were believed to cause abnormal behavior, especially hyperactivity in normal children, those with ADD, and in juvenile delinquents. The misnomer "sugar allergy" was coined. DBPCFC studies have documented the fact that sugar in the diet does not have an adverse effect on behavior and, in some cases, may have a calming effect. In the 1960s, D. Pearson coined the term pseudo-food allergy to describe a syndrome that usually occurs in adults who believe they have food allergy and restrict their diet to such a degree that they develop signs of malnutrition (*see* Table 2). Almost all the patients who have been reported with this condition have

been found to have psychological problems, especially depression. The symptoms they complain about include fatigue, headaches, "mental fuzziness," malaise, arthralgia, and myalgias. When DBPCFC studies were done, none of the patients studied reacted to the foods to which they were supposedly sensitive. With psychological counseling, all resumed a normal diet without adverse effect.

DIAGNOSIS OF FOOD ALLERGY OR INTOLERANCE

History

As outlined in Table 4, a good history is the most important factor in diagnosing a food allergy or intolerance. The history should include:

1. The description of the problem;
2. The timing of the onset in relationship to the specific food or additive in the diet and the duration of the event;
3. The frequency of symptoms (continuous or intermittent in nature); and
4. Other circumstances.

Most individuals who develop food allergies have other manifestations of allergy personally or have family members with allergic disease. This includes atopic dermatitis, urticaria, asthma, allergic rhinitis/conjunctivitis. A history of asthma in a food allergic individual should be considered a risk factor for possible serious life-threatening reactions of an anaphylactic nature to that food.

Certain foods are associated with different types of allergic and intolerance reactions (*see* Table 3). This should be kept in mind when taking a history of the presenting complaint. Most food anaphylactic reactions (e.g., urticaria or systemic anaphylaxis) occur within minutes (and almost always within 2 h) after exposure to the food. In these types of cases, it is often easier to pin down a likely food candidate because of the closest association in time. More difficult are cases in which the problem is chronic (e.g., atopic dermatitis) and in which many nonallergic factors play a role. In studies involving children who were allergic to food and had atopic dermatitis, the patient's history of the likelihood of a specific food being involved was often not helpful. Food allergy skin testing or in vitro IgE-specific food antibody testing was more helpful in narrowing down the field of likely foods responsible for the allergic reaction. Finally, being a "good detective" may take a lot of time, especially when the culprit food responsible for the adverse reaction is not obvious and/or a part of a prepared food.

IgE Food Allergy Skin Testing or In Vitro Food Allergen-Specific Antibody Testing

Only the epicutaneous (prick/scratch/puncture) type of immediate reacting IgE (allergy) skin testing is used to diagnose food allergy. Tests are done with a drop of food allergen concentrate (usually 1:10 weight by volume) on the forearm or back and read in 15 min. Either commercial allergy extract or fresh material (e.g., juice from a fresh apple in the oral allergy syndrome) can be used. Reactions in which the wheal is measured at 3 mm or more than the negative saline control are considered to be positive.

Table 4
Diagnosis of Food Allergy and Intolerance

History	Description of problem
	Timing of onset and duration of event related to diet
	Frequency of symptoms
	Other important circumstances
IgE-reacting skin testing and in vitro IgE antibody testing	
Food diary and diets	
Confirmatory food challenges	Open
	Double-blind, placebo-controlled
Other tests	Mast cell tryptase
	Analysis of potential food allergen ingredient content in processed foods
	Breath hydrogen and lactose tolerance

Confirming the Diagnosis of an Adverse Food Reaction

- A DBPCFC is the "gold-standard" for the diagnosis of an adverse reaction to food.
- A positive DBPCFC does not identify the mechanism of reaction.
- In most cases of systemic (life-threatening) anaphylaxis, a DBPCFC is not clinically necessary since it is risky; the presence of IgE allergen-specific antibody can help establish a "presumptive" diagnosis
- Food diaries and short-term elimination diets at home may be helpful tools, but in themselves do not confirm the diagnosis
- IgE food prick tests or in vitro assays may assist the clinician in narrowing down the field of likely foods in suspected food allergy

In vitro IgE food allergen-specific antibody testing either the radioallergosorbent test or the enzyme-linked immune assay methods are used. The in vitro tests are less sensitive than the skin test for foods and do not give more information (if the skin test is negative). The in vitro assay is the diagnostic method of choice in cases of systemic anaphylaxis, since it is safer. In these situations, any individual who had a recent systemic anaphylactic reaction to a food (e.g., peanut), is likely to have enough IgE-specific antibody in the serum to give a positive in vitro test.

The food allergy skin test (or in vitro test) is helpful to screen for food allergies. If one of these two tests is positive in infants, there is up to a 50% chance (for commonly eaten food) that the individual, if challenged, would be actually found to be clinically sensitive to that food. If the in vitro test is positive, there is approx a 40% chance that the individual, if challenged, would actually be clinically sensitive to food. If the skin test or the in vitro allergy food tests are negative, however, almost 100% of the time if one would challenge with that food the challenge would be negative.

If either the immediate food allergy skin test or the IgE food allergy-specific in vitro test is positive in adults (where the frequency of true food allergies are less common than in infants and children) with any food there is only a 3% chance that if the adult were challenged with the food, it would be clinically relevant. Again, if either the food skin test or the in vitro test is negative in adults, there is close to a 100% chance that a food challenge would be negative. In the case of systemic anaphylactic reactions to food, usually the in vitro allergy skin test is positive in a presumptive diagnosis of food anaphylaxis if made without any confirmation challenge studies.

Food Diary and Diets

Food diaries may be helpful in the situation of the patient who presents with a history of several, but intermittent, episodes of acute urticaria. If there is no obvious etiology, a diary of events, including a diet for subsequent episodes, may be helpful in pinning down the ultimate diagnosis.

Temporary use of diets composed of foods to which most individuals have no allergy or intolerance is sometimes helpful when the patient presents with a chronic problem, suspected of being related to diet, but not involving anaphylaxis. Examples of these allergy-free diets can be found in numerous textbooks and in Table 5. Usually the patient is kept on such a diet for 2 wk and then one new food is added to the diet every 3 d (and the previously added food is kept in the diet—providing no adverse symptoms occurred). This is continued until a normal diet has been resumed.

Food Challenges

It is usually advisable to refer problem patients potentially requiring food challenge to an allergist/immunologist for evaluation. The gold standard in substantiating an adverse reaction to food regardless of the etiology is the DBPCFC. Usually if a food challenge confirmation is necessary, an open food challenge is done first under controlled conditions, followed by at least a 2-h wait. In most clinical situations, no challenge is indicated if the situation involves systemic anaphylaxis. A good history backed up by the finding of IgE antibody to that food in in vitro testing is enough for presumptive diagnosis. If open challenge is positive, to make absolutely sure of the etiology of the reaction the DBPCFC technique is advised (*see* Table 6 for this procedure). Details on the use of this type of challenge can be found in standardized textbooks.

Other Tests

Serum mast cell tryptase is a helpful tool in diagnosing serious systemic anaphylaxis and anaphylactoid reactions (*see* Chapters 5 and 16). Usually this enzyme is present in the blood for up to 2 h after the event, about the time when the patient is seen by a physician in an emergency situation. Unfortunately, in many cases of anaphylaxis owing to food, blood mast cell tryptase elevation cannot be detected. Therefore, if the enzyme is detected (test is positive), it is helpful information. If the test is negative, however, it does not rule out a systemic food reaction.

In some situations it is necessary to do a detailed analysis of a meal or processed foods, using immunologic techniques in order to pin down a particular type of food protein suspected as being responsible for an allergy or an intolerance. Even trace amounts

Table 5
Major Food Allergen-Free Diet
Foods and Beverages Allowed[a]

Apricots	Chicken	Pineapple	Sugar (cane or beet)
Arrowroot	Ginger ale	Plums	Sweet potatoes
Artichokes	Ham (boiled)	Poi	Tapioca (whole or pearl, not minute)
Asparagus	Kidney beans	Potatoes	Turkey
Bacon	Lamb	Potato chips	Vanilla extract
Beef, all-beef wieners	Lentils	Prunes	Water
Beets	Lettuce	Rice	White soda
Blueberries	Maple syrup or maple-flavored cane syrup	Salt	White vinegar
Carrots		Soybeans	Yams
Celery	Navy beans	Soybean sprouts	
Cherries	Olive oil	Soy milk	
Any vegetable shortening or oleomargarine that contains no milk		Spinach	

[a]All fruits and vegetables, except lettuce, must be cooked.

Table 6
DBPCFC Guidelines[a]

The challenge should be performed by personnel knowledgeable in the management of anaphylaxis
The procedure should be done under controlled conditions, in the hospital, clinic, or office
The suspected food should be eliminated from the diet 10–14 d prior to challenge
Antihistamines should be discontinued 12 h prior to challenge
The individual to be challenged should be in a stable cardiovascular, pulmonary, and metabolic condition prior to challenge
The individual to be challenged should be in a fasting state (6–12 h) when challenged
The challenge should start with a low dose (e.g., 125–500 mg of lyophilized food) so as **not** to provoke symptoms
Gradual increases in dose (suspected food or placebo) should occur by doubling the amount every 15–20 min
The maximum dose of food used in challenge should approximate 10 g of lyophilized food
The minimum recommended observation period following completion of the DBPCFC procedure for:
- Suspected anaphylaxis is 2 h
- Isolated GI signs/symptoms is 4–8 h
- Food intolerance reactions is 4–8 h

In followup of negative specific food challenge, open feeding with this food is recommended for the subsequent 24–48 h

[a]Sampson HA, Metcalfe DD. Food allergies. *JAMA* 1992; 268: 2840–2844.

of food protein may be important in precipitating anaphylaxis in very sensitive individuals. The label on processed foods may not indicate a contaminant or an offensive food protein that ended up in the final product through some misadventure during the food processing. In lactose intolerance (commonly mistaken for cow's milk allergy), confirmation of this idiosyncratic reaction can be done using either breath-hydrogen analysis or lactose-tolerance testing.

MANAGEMENT OF FOOD ALLERGY OR INTOLERANCE

The management of proven or suspected food allergy is strictly to avoid that food. In some food-intolerance reactions, such as lactose intolerance, the reaction is quantitative, since that, in small amounts, lactose sugar-containing foods can be tolerated. This is in contrast to the case of systemic anaphylaxis, where food allergens in trace amounts can trigger a serious life-threatening event once the patient is sensitized and preformed IgE antibodies exist to that food.

Long-term specific food avoidance may be a problem for patients, especially when they are away from home, while at school, eating in the cafeteria, at a restaurant, or at a party. Some foods, like nuts and peanuts, are easily disguised in candies, bakery products, hors d'oeuvres, or in salads or salad dressings. The cooking steam from fish or seafood may precipitate a reaction for specifically sensitive individuals. Processed foods may not have detailed labeling to identify a dangerous food. Detailed ingredients in a restaurant meal may be difficult to identify (it is usually not advisable to take the waiter's viewpoint—only the cook knows).

In a situation where a definite food allergy is known or a presumptive diagnosis has been made, it is best for the individual to carry an Epi-Pen™/Epi E-Z Pen™ (0.3 mg) or an Epi-Pen Jr.™/Epi E-Z Pen Jr.™ (0.15 mg) and to wear medical alert jewelry about that sensitivity or intolerance (*see* Table 7). Patient information concerning food allergies and food intolerance can be obtained through the Allergy Food Network or Asthma and Allergy Foundation of America (AAFA).

Allergen immunotherapy has been used to treat other allergic diseases, such as allergic rhinitis. Although food allergen injection therapy using conventional methods has been used experimentally, this treatment method is not clinically accepted. The alternative medicine practice of either using injections or food drops to neutralize symptoms as methods to prevent food reaction symptoms are **unproven** and **unapproved** treatments.

Infant Formula Substitution

A particular problem exists for infants who are allergic or intolerant to conventional cow's milk-based formula. Although some individuals who are milk allergic and have urticaria can use a soy-based formula substitute, any child with a GI problem should be placed on a casein protein hydrolysate infant formula. Nutramigen™ (or Alimentum™) is usually preferable to Pregestimil in the United States. A few infants who are very sensitive to cow's milk protein and cannot tolerate a protein hydrolysate formula should be tried on elemental amino acid formula (Table 8). The only one on the US market that is designed for infants is Neocate.™

Table 7
Management of Food Allergy or Intolerance

Strict avoidance of the offending food (anaphylaxis) or in *small amounts* (some food intolerances)
Food substitution (e.g., infant formula)
Future role of allergen immunotherapy
In case of systemic anaphylaxis:
  Epi-Pen or Epi E-Z Pen autoinjector (0.3 cc 1:1000 aqueous epinephrine) or Epi-Pen Jr or Epi E-Z Pen Jr. (0.15 mg epinephrine) (1:2000)—use in < 6 yr of age) (Center Labs, Port Washington, NY)
Systemic anaphylaxis: Medic Alert jewelry (Medic Alert Foundation, Turlock, CA)
Patient support
  Food Allergy Network
  4744 Holly Avenue
  Fairfax, VA 22030
  (703) 691-3179; fax (703) 691-2713
  Asthma and Allergy Foundation of America (AAFA)
  1125 Fifteenth Street NW
  Suite 502
  Washington, D.C. 20005
  (800) 727-8462

Table 8
Commercial Substitutes Infant Formula for Milk-Allergic and Intolerant Children

Cow's milk-based
  Casein protein hydrolysate
    Nutramigen[a]
    Progestamil[a]
    Alimentum[b]
  Whey hydrolysate
    Carnation Good Start[c]
  Soy protein-based
    Numerous, such as Isomil,[a] Pro SoyBee[b]
  Elemental amino acid-based
    Neocate[d]

[a]Mead Johnson, Evansville, IN 47721.
[b]Ross Lab., Columbus, OH 43216.
[c]Clintec Nutrition Co., Deerfield, IL 60015.
[d]Scientific Hospital Supplies, Inc., Gaitherburg, MD 20877.

Prevention of allergy has been attempted in infants born to allergic parents by the use of special diets. When studies have compared the use of:

1. Dietary restriction in the mother in the last trimester (of a diet devoid of allergy-type foods);
2. breast feeding; or

3. casein hydrolysate formula feeding in the infant; and
4. avoidance of allergic-type solid food in the infant for 1 year to conventional formula feeding, the specially fed infants had less food-related allergy symptoms for the first 2 yr of life than infants who were fed conventional diets. However, at 2 yr, there was no difference in the overall allergic symptoms between the two groups.

The whey hydrolysate formula "Carnation Good Start" instead of conventional cow's milk formula is not a good substitute for individuals proven to be allergic to cow's milk, since serious reactions may occur. This formula, however, has shown to be less allergic than conventional cow's milk infant formula. Therefore, this type of feeding as an alternative to prolonged breast feeding (9 mo), is a suitable preventive measure in an infant born to allergic parents to reduce possible food allergy symptoms in the first 2 yr of life.

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16 Allergic and Allergic-Like Reactions to Drugs and Other Therapeutic Agents

John A. Anderson, MD

CONTENTS

INTRODUCTION

Definition

Drug allergy is often a common term used to depict any unexpected and unwanted event or effect that occurs when an individual is taking a specific drug or therapeutic agent. A better, overall term to describe these circumstances would be an adverse reaction to a drug (*see* Table 1).

These reactions can be further classified into either drug allergy (reactions owing to an immunologic mechanism) or drug intolerance (reactions owing to nonimmunologic or unknown mechanisms). Some reactions closely resemble allergic reactions and are termed "allergic-like" or pseudo-allergic. This includes anaphylactoid reactions that clinically resemble anaphylaxis, since in both situations, chemical mediator release or activation is responsible for these symptoms. Some idiosyncratic reactions to drugs can be confused with drug allergy.

From: *Allergic Diseases: Diagnosis and Treatment*
Edited by P. Lieberman and J. Anderson Humana Press Inc., Totowa, NJ

Table 1
Definition of Terms Used to Describe Adverse Reactions to Drugs and Therapeutics

Drug allergy: drug reactions resulting from an immunologic mechanism
Drug intolerance: adverse reaction to drugs resulting from nonimmunologic or unknown mechanisms
- Drug overdose: toxic reaction owing to excess drug dose or impaired excretion
- Side effect to a drug: unavoidable secondary pharmacologic action of a drug
- Drug interactions: actions of two or more drugs on the toxicity or effects of each individual agent
- Idiosyncratic drug reaction: a measurable, abnormal response to a drug that differs from its pharmaceutical effect

Other terms used to describe allergic/intolerant reactions
- Allergic-like or pseudo-allergic reactions to drugs: drug reactions that clinically resemble those of drug allergy; the mechanism usually involves clinical mediators or activators, enzyme inhibition, or may be unknown
- Anaphylaxis and anaphylactoid reactions to drugs: generalized drug reactions owing to chemical mediator release/activation either involving IgE (anaphylaxis) or direct action of the drug on the mast cell (anaphylactoid)

Classification

Because of the different mechanisms involved in adverse reactions, it is impossible to classify all reactions to drugs and therapeutic agents under one heading. Table 2 classifies adverse reactions to these agents under four categories: generalized, immunologic, organ-specific, and allergic-like reactions. A specific drug reaction may be classified under more than one category.

Incidence

The exact incidence of all types of adverse reactions to drugs and therapeutic agents is unknown. However, it is estimated that 1–2 million individuals in the United States experience a drug reaction each year. The most frequent manifestation of a drug reaction is a skin rash. Studies have shown that 2% of adult medical admissions each year to a community hospital are the result of drug reactions. Studies involving adults admitted to either medical or surgical wards in tertiary care hospitals demonstrate a 6.5% yearly adverse reaction rate. Of these, 1% were fatal, 12% were life-threatening, and 30% were serious. Most drug reactions involve nonimmune or unknown mechanisms and are thus defined broadly as drug intolerances, not drug allergies (*see* Table 1).

In the case of two types of drug reactions, penicillin and other β-lactams, as well as conventional radiocontrast media (RCM), the incidence of allergic and allergic-like reactions have been calculated. The risk of developing an allergic reaction, usually a rash, to a single course of penicillin is 2% and to cephalosporin is 2–3%. The risk of developing anaphylaxis to penicillin is no more than 0.04% (1/2500 courses of the drug), but it is rare to have such a reaction with a third-generation cephalosporin. Fatalities to penicillin are unusual. The risk ranges between 0.0015 and 0.002% (1 death/50,000–75,000 courses of the drug).

Table 2
Classification[a] of Different Manifestations of Adverse Reactions to Drugs or Therapeutics

Generalized reactions
Mast cell-derived mediator reactions
Systemic anaphylaxis and anaphylactoid reactions
Generalized urticaria and angioedema
Serum sickness reactions
Drug fever
Drug-induced vasculitis
DLE
Autoimmune drug reactions
Immunologic reactions
Type I—IgE-antibody-mediated (e.g., β-lactam antibiotics, insulin urticaria, or anaphylaxis)
Type II—antitissue cytotoxic antibodies (e.g., drug-induced hemolytic anemia or thrombocytopenia)
Type III—antigen–antibody immune complex involving complement reactions (e.g., serum sickness-like drug reactions)
Type IV—cell-mediated hypersensitivity (e.g., neomycin contact dermatitis)
Organ-specific drug reactions
Skin (e.g., pruritus, maculopapular, morbilliform and erythemic rashes, urticaria/angioedema, erythema multiform, fixed drug eruptions, phototoxic and photoallergic reactions)
Blood (e.g., drug-induced hemolytic anemia, thrombocytopenia)
Liver (e.g., hepatitis)
Lung (e.g., fibrosis)
Kidney (e.g., nephritis)
Pseudo-allergic (allergic-like) reactions
Ampicillin/amoxicillin rash
RCM reactions
Reactions to aspirin and nonsteroidal anti-inflammatory agents
Reactions to enzyme inhibitors (e.g., ACE inhibitor-induced angioedema)
Reactions involving histamine release (e.g., vancomycin red man syndrome)

[a]A specific drug reaction may be classified under more than one category.

Overall reaction rates to conventional RCM (high molarity) have been reported to range from 4.6 to 8.5%. Anaphylactoid reactions occur in 1% or less of patients receiving RCM and fatalities have been reported to be as many as 0.009% (1/11,000 procedures). Overall reaction rates to lower-molarity RCM have been less than conventional high molarity material and have been reported to be approx 2%. Serious reactions to RCM that require subsequent hospitalizations are estimated to be 1/2900 conventional RCM infusions and 1/8400 infusion with the low-molarity RCM. Death from convention RCM is reported to be 1/10,900, but rare with low-molarity RCM use (1/165,000–500,000 procedures).

Table 3
Factors Influencing the Frequency of Adverse Reactions to Drugs and Therapeutic Agents

Drug type	Familial history of reactions
Degree of drug exposure	Atopy
Routes of administration	Viral infections
Age and sex	Concomitant drug use

Factors That Influence Incidence

Table 3 lists important factors that may influence the likelihood of an adverse reaction during the use of a drug or therapeutic agent. Some drugs are more likely to be involved in reactions than others. Antibiotics, especially β-lactams and sulfonamides, followed by aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) and central nervous system (CNS) depressants, are most commonly involved in these serious reactions. The β-lactam antibiotics, trimethoprim sulfamethoxazole (TMP-SMX), and whole blood are most likely to be involved in skin rashes, the most common manifestation of adverse reactions. Minor drug reactions (e.g., nausea) are more often involved with narcotic use, antibiotics, and cardiovascular drugs.

Allergic sensitization to drugs is more likely to occur after multiple, intermittent courses of a drug than with continuous administration of that drug. All types of reactions to medicine occur more often when patients are treated with multiple agents than with single agents. Allergic drug sensitization is most likely to occur during topical exposure and least likely to occur with oral administration. Once sensitization has occurred, however, elicitation of a drug reaction on reexposure to that drug may occur by any route, but the oral route is the safest, and the intramuscular route (im) is more risky than the intravenous (iv) route.

There are probably more adverse drug reactions in the elderly, and drug skin rashes are reported to be one-third higher in females. Individuals who have a severe reaction to one drug (e.g., β-lactam antibiotics) are at increased risk for reactions to other antibiotics. Children of parents with a confirmed reaction to a β-lactam antibiotic have more risk than the general population to develop an allergic reaction to β-lactam antibiotics. Although being "allergic" or atopic does not increase the risk of development of an allergy to β-lactam antibiotics, it may increase the risk of having an anaphylactoid reaction to RCM exposure.

A maculopapular (toxic) rash caused by Amoxicillin/ampicillin is more likely to occur when the patient treated with this drug has an Epstein-Barr virus infection (acute infectious mononucleosis). Both drug allergies (e.g., to β-lactam antibiotics) and drug intolerance reactions (e.g., systemic or skin reactions to many types of therapeutic agents) are more likely to occur in patients afflicted with the human immunodeficiency virus (HIV) than HIV-seronegative individuals. The risk of drug reactions increases with the degree of immunosuppression. Concomitant administration of a β-blocking adrenergic drug increases the risk of both anaphylaxis to β-lactam antibiotics and the seriousness of anaphylactoid reactions in RCM.

Overview of Adverse Drug Reactions

- Most reactions do not involve immune events.
- A skin rash is the most common type of drug reaction.
- Most drug reactions occur in adult females and those individuals who are frequently intermittently exposed to multiple medications.
- More allergic drug reactions occur to β-lactam antibiotics than to other antibiotics.
- Reactions to RCM and aspirin/nonsteroidal anti-inflammatory agents are frequent causes of allergic-like or nonimmunologic reactions.

MECHANISMS OF ALLERGIC AND ALLERGIC-LIKE REACTIONS TO DRUGS AND THERAPEUTICS

The exact mechanism involved in most reactions to drugs and therapeutic agents is unknown. Fully 90% of adverse reactions fall into the drug intolerance group. Of those reactions that are classified as a drug allergy, the best-studied reactions are those to β-lactam antibiotics, particularly penicillin as well as insulin.

β-Lactam Antibiotics

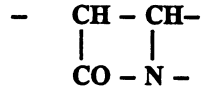
β-lactam antibiotics include the penicillins, cephalosporins, carbapens, and monobactams. These drugs have a common β-lactam ring chemical structure (*see* Fig. 1). In the human body, penicillin is metabolized to form various products (*see* Fig. 2). Most of the parent drug is broken down into penicilloyl, which readily combines with a carrier protein to become a complete antigen. This is called the major determinant (most common metabolic byproduct). The remainder of penicillin stays either in its native state or is metabolized to other chemical structures, such as penicilloate or others. These agents, coupled with a protein, are referred to as minor determinants (less common metabolic byproducts).

The ease with which these penicillin metabolites and the parent penicillin couple to tissue proteins is believed to be important regarding why these drugs are so often involved in allergic reactions and other drugs are not.

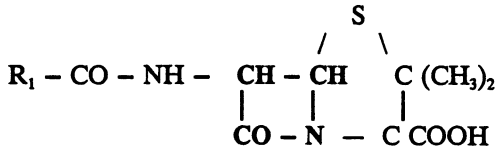
In individuals who have become allergic to penicillin, most develop Type I (*see* Table 2) IgE-specific reactions to the major determinants alone or in combination with sensitization with the minor determinant—not sensitization to the minor determinants alone. In individuals sensitized to the major determinant, urticarial rash is the usual manifestation. In individuals sensitized to the minor determinant, specific systemic anaphylaxis is more of a risk.

Penicillin and other β-lactam antibiotics may also be responsible for a Type II or Type III immune reaction (*see* Table 2). Immune hemolytic anemia can result from the binding of the drug or its metabolites to the surface of a red cell, followed by a specific antibody-mediated cytotoxic reaction that is directed against the drug antigen or at the cell membrane component altered by the drug. This reaction and immune thrombocytopenia may occur with other drugs as well.

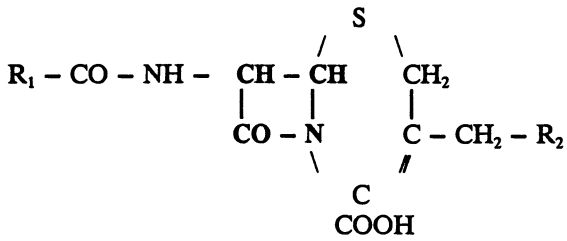
BETA LACTAM CHEMICAL STRUCTURES



Beta Lactam Ring



Basic Penicillin



Basic Cephalosporin

Fig. 1. β-Lactam chemical structures.

In Type III immune reactions, soluble immune complexes are responsible for the syndrome of serum sickness. Although originally this term depicted reactions to "horse serum," penicillin and other β-lactams as well as other drugs can react in a "serum sickness-like" fashion. Clinically, events are characterized by a fever and a rash that includes a papular urticaria and/or urticaria, lymphadenopathy, and arthralgia, which occur 2–4 wk after beginning the drug therapy. At this point, drug and drug antibody immune complexes are in slight antigen excess, and the complement system is activated. Clinical symptoms of serum sickness begin to subside when the drug/metabolites are eliminated from the body by the reticuloendothelial system.

Insulin

Human insulin has a mol wt of approx 6000, and its amino acid sequence differs from pork insulin by only one amino acid and beef insulin by three amino acids. Animal-derived insulins make up the majority of replacement insulins used today in the United States. Insulin is a potent antigen. About one-half of humans receiving

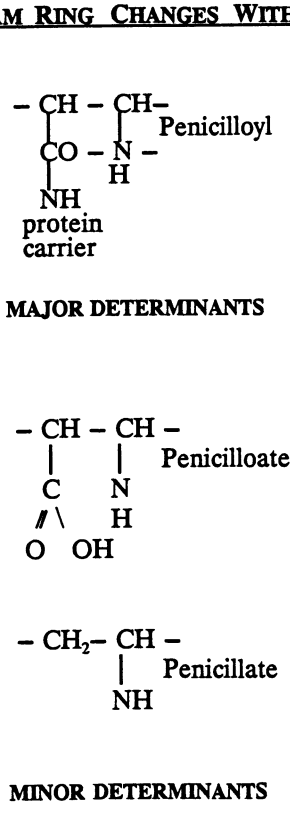


Fig. 2. β-Lactam ring changes with metabolism.

regular insulin therapy develop IgE antibodies. The antibodies are directed against the insulin molecule itself, even though animal-derived insulin contains other proteins that may stimulate an immune reaction. These individuals will have positive IgE allergy skin tests. Only 5%, however, will have severe enough local reactions at the injection site to be clinically relevant, and 0.1–0.2% may develop systemic anaphylaxis to insulin.

RCM

The imaging efficacy of RCM depends on the iodine concentration that can be delivered to a space within the body. Since RCM was first discovered in 1923, the character of the iodinated compound has progressed from a monoiodinated to a tri-iodinated benzoic acid compound. The conventional RCM is hypertonic, having an osmolarity up to six times that of plasma. A newer, nonionic RCM has been developed that has an osmolarity <50% of the conventional material and retains the same iodine concentration. This change in osmolarity of the newer RCM material has reduced the allergic-like toxicity of these agents, presumably by reducing the capacity of the newer agent to form bonds with body proteins.

The exact mechanism by which RCM elicits an anaphylactoid reaction is unknown. However, in vitro histamine release does occur, probably through direct interaction between RCM and a cell membrane receptor. Unfortunately, there is no consistent documented relationship between histamine release by these agents and clinical adverse events.

RCM can activate the complement system. Conventional RCM has been shown to have a direct effect on C-3 and C-4 to produce C3b and C4b anaphylactoxins (which in turn can cause histamine release). The newer low-osmolarity RCM has been shown to activate complement through the alternate pathway by inhibition of factors H and I. The exact role activation of complement by either conventional or the newer RCM agents plays in the production of an anaphylactoid reaction is still speculative.

Mechanisms of Other Drugs Involved in Allergic-Like Reactions

Aspirin is responsible for triggering asthma and urticaria. To a lesser degree, NSAIDs may also precipitate these events. These drugs are responsible for a syndrome consisting of perennial rhinitis, sinusitis, nasal polyps, and severe asthma. Current studies indicate an important role for increased leukotriene production (especially LTC4, LTD4, and LTE4), kininogens, and histamine release in these allergic-like reactions.

Vancomycin antibiotic IV infusion has been responsible for a generalized flushing, the so-called red man syndrome. The mechanism of reaction in this case is thought to be related to direct toxic release of histamine from mast cells/basophils. Angiotensin-converting enzyme (ACE) inhibitors are now commonly used antihypertensive agents. This group of agents has been associated with both a maculopapular rash and angioedema (anaphylactoid reactions). Although the mechanism of the reaction is not entirely clear, increased histamine release, inhibition of bradykinin degradation, and abnormal prostaglandin and substance P metabolism are suspected. Blood products and protamine sulfate (fish-derived protein), which is a component of some insulin preparations and is an anticoagulant, may result in anaphylactoid reactions through activation of the complement system and release of anaphylactoxins (C3a and C4a).

SIGNS AND SYMPTOMS OF ALLERGIC AND ALLERGIC-LIKE DRUG REACTIONS

Generalized Reaction

Anaphylaxis and anaphylactoid reactions to drugs and other therapeutic agents have the same signs and symptoms of reactions as other agents that frequently cause allergic reactions (e.g., insect stings, foods, natural rubber latex). Reactions range in severity from mild pruritus, skin erythema, and urticaria/angioedema to more generalized and systemic reactions of laryngeal edema, rhinitis/conjunctivitis, asthma, shock, and possibly death. IgE sensitization is involved with the following drug reactions: β-lactam antibiotics, insulins, protamine, blood products, chymopapain, vaccines, natural rubber latex used in drug delivery systems, ethylene oxide used to clean dialysis agents, or neuromuscular agents used in anesthesia induction. Anaphylactoid reactions may occur to RCM, ASA, NSAIDs, Ace inhibitors, Vancomycin, and blood products.

Other generalized allergic-like drug reactions (*see* Table 2) include serum sickness, in which the symptoms begin 7–21 d into drug therapy. These drug-induced serum

Urticaria and Drug Reactions

- Severe urticaria may be a manifestation of cutaneous (mild) anaphylaxis/or anaphylactoid reactions.
- Urticaria is suggestive, but not diagnostic of an allergic etiology.
- Urticaria may be caused by other factors, such as viral infections.
- A drug-induced skin rash that does not include urticaria does not rule out immunologic involvement.

sickness-like reactions are characterized by fever, malaise, urticaria, arthralgia, and lymphadenopathy. Reactions occur not only to blood products, but also to β-lactam antibiotics, sulfonamides, thiouracil, cholecystographic dyes, hydantoin, aspirin, and streptomycin as well as other agents.

Isolated drug fever typically occurs between the 7th and 10th d of therapy and may occur with many drugs, especially antibiotics and blood products. Drug-induced lupus erythematosus (DLE) is usually characterized by mild fever, malaise, and arthralgias. Butterfly rashes on the face, renal, CNS involvement, and Renaud's phenomenon are less common in the drug form than in the idiopathic systemic form of the disease (SLE). The drugs usually involved with this condition include procanamide, hydralazine, isoniazid, chlorpromazine, and hydantoin. The signs and symptoms usually improve or decrease with discontinuation of the specific drug involved.

Isolated Skin Reaction

Isolated skin lesions to drugs are the most common adverse symptoms of drug reactions. Almost any type of manifestation can occur (*see* Table 2). However, a maculopapular/morbilliform rash is the most frequent, followed by urticaria in allergic or allergic-like reactions. Usually drug reactions are symmetrical and begin in the extremities in the ambulatory patient or on the back in bedridden patients. The ampicillin/amoxicillin rash typically occurs on the knees and elbows first, before spreading over the body. Urticaria/angioedema occurs with all types of reactions, including drug allergy, drug intolerance, and infections. A fixed drug eruption is a rare localized patch of eczema that reappears at the same site with repetitive drug treatment. Many drugs can be involved, but the reaction is more commonly associated with phenobarbital or antibiotic treatments.

Phototoxic (sunburn-like) rash may occur with short-term sun exposure while patients are on such drugs as doxycycline or chlorpromazine. Prolonged sun exposure may produce a photoallergic (urticarial or eczema) rash when individuals are on such drugs as griseofulvin, psoralens, and sulfonamides.

Erythema multiforme (EMminor) "target" skin lesions as well as the combination of EM (major) fever, toxicity, and ulceration of the mucous membrane (Stevens-Johnson Syndrome [SJS]) or sloughing of the skin (toxic epidermal necrolysis[TEN]) may be both drug- and viral-infection-associated. No immune reaction has been identified in these reactions. EM minor is a mild condition, and the mortality of SJS is low. The mortality of TEN, however, may be as high as 30%, especially in the elderly. Drugs that have been repeatedly involved include the sulfonamides (especially TMP-SMX)

Febrile Mucocutaneous Reactions

- Includes Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)
- Syndrome consists of fever, erythema multiform rash, and ulceration of two or more mucous membranes, plus with TEN, skin sloughing
- SJS and TEN are frequently drug-associated; however, these reactions may be precipitated by viral infections and other unknown events
- If drug-associated, repeat exposure to the same drug is contraindicated

seizure medications and β-lactams antibiotics. Drugs that have been associated with EM minor or systemic reactions (e.g., SJS or TEN) should be strictly avoided, since re-exposure may be associated with a more serious reaction.

Signs and Symptoms of Other Organ-Specific Reactions

Type II immune reactions (*see* Table 2) to such drugs as β-lactam antibiotics may result in a hemolytic anemia, usually 7 d after beginning therapy. Quinine, quinidine and sedormid have been involved in immune thrombocytopenic-type reactions. Hepatitis has been shown to occur with several drugs, including sulfonamides, phenytoin, and halothane. Methicillin as well as sulfonamides have been involved in producing interstitial nephritis in rare patients. Phenytoin and gold have been involved in reactions characterized by systemic eosinophilia and pneumonitis.

GENERAL APPROACH TO THE DIAGNOSIS AND MANAGEMENT OF ALLERGIC AND ALLERGIC-LIKE REACTIONS TO DRUGS AND THERAPEUTICS

Initial Measures

Initially, when an adverse drug reaction is suspected, especially when associated with significant symptoms, the drug should be discontinued (*see* Table 4). Any treatable signs and symptoms should be then promptly attended to. Simple pruritus and urticaria with or without angioedema will usually improve with an antihistamine (e.g., 10–25 mg of hydroxyzine—Atarax pr 25–50 mg of diphenhydramine—Benadryl, 2–4 times daily). Initially, aqueous adrenalin 1:1000, 0.1–0.3 cc subcutaneously followed by susphrine 1:200 0.05–0.15 cc subcutaneously will help the pruritus and the acute rash in an office or emergency room situation. Treatment of acute systemic anaphylaxis or anaphylactoid reactions from any cause is outlined in Chapter 5.

There are few (if any) absolute confirmatory tests available initially when an adverse reaction involves mediator release, is to a drug is suspected. Diagnosis is usually, therefore, presumptive. Management is important in spite of this fact (e.g., drug discontinuation, treatment of signs and symptoms of the reaction, substitution of another drug if necessary).

One helpful test (if positive) that can help confirm the fact that the reaction involves mediator release is an in vitro mast cell tryptase blood test. In severe cases of systemic anaphylaxis/anaphylactoid reactions, tryptase is released along with other

Table 4
General Approach to Diagnosis and Management of Allergic Drug Reactions

Initial measures
1. Discontinue suspected medication
2. Treat reaction
3. Draw blood for possible confirmation of etiology in select situations (e.g., tryptase in anaphylaxis/anaphylactoid reactions; C levels in serum sickness, Coomb's test in hemolytic anemia)
4. Substitute appropriate medication whenever possible
5. In very select cases and when appropriate, desensitize with original medication if no substitute is available (e.g., β-lactam, insulin, TMP-SMX, ASA)

Followup measures
- Skin test in case of drug allergy (e.g., β-lactam antibiotics,[a] insulin, papain,[a], and latex)
- Skin test/subcutaneous drug challenge (local anesthetics)
- Oral sequential challenge under controlled conditions (nonanaphylactic conditions)
- Strict avoidance based on presumptive diagnosis
- Preventative measures for inadvertent exposure in serious situations (e.g., Medic Alert, Epi-Pen auto injector)

[a]In vitro tests available to some degree.

mast cell chemical mediators. This enzyme remains elevated in the bloodstream for several hours after the event, thus allowing the possibility of confirming a mast cell degranulation (and histamine and other mediator involvement) in the reaction at the time that the patient is seen in the office or emergency room for the acute symptoms.

When serum sickness is suspected, the complement system is usually activated and low serum levels of C3, C4, and possibly Ch50 may, in retrospect, help confirm the suspicion of this condition. In cases of hemolytic anemia, a positive Coombs test will help confirm the immune nature of this condition.

In almost all cases, the drug or therapeutic agent presumed to be responsible for the adverse reaction can be avoided and a substitute medication should be available to treat the primary condition. Occasionally, this is not possible if the primary condition is serious and the offending drug is important to therapy. In some of these cases, drug desensitization is possible.

Followup Measures

Elective immediate reacting allergy skin testing is usually only available in the case of β-lactam antibiotic sensitivity, insulin sensitivity, and with natural rubber latex. It is available experimentally for papain sensitivity and suspected sensitivity to neuromuscular blocking agents. In vitro blood/serum assays are only available for latex, β-lactam antibiotics (penicillin major determinant only), and papain (experimental). These in vitro assays are only helpful if positive. A negative test does not rule out sensitivity. At one time, in vitro cell-mediated drug lymphocyte transformation testing was available in some experimental laboratories. There is little or no current evidence regarding the value of this type of drug reaction testing today. In cases of suspected local anesthetic reactions, a well-studied protocol consisting of skin testing

followed by a graded sc injection challenge helps confirm the safety of local anesthetics for subsequent use.

In some cases, when adverse symptoms are minor (maculopapular rash to an antibiotic that is usually not associated with systemic anaphylaxis or anaphylactoid reactions), a graded oral challenge may be done on an outpatient basis. When done, however, it should be done under controlled conditions where the physician is prepared to manage the possibility of a serious reaction (e.g., systemic anaphylaxis). Usually the total amount challenged under these conditions is the amount of a usual single dose (e.g., 250–500 mg of an antibiotic in an adult). The patient should wait for at least 2 h following challenge before going home. Usually, it is advisable to avoid starting therapeutic doses of the antibiotic until the next day (12–24 h) after challenge, providing no adverse reaction occurs during the interval.

In most cases, after a presumptive diagnosis of drug allergy or intolerance has been made, the individual is advised to avoid these medications. In some cases of reactions to drugs, drug desensitization is possible and necessary. In the case of anaphylaxis/anaphylactoid reactions and other serious systemic events (e.g., SJS or TEN), re-exposure to the medication is not advised.

In situations where there is a documented life-threatening drug reaction (e.g., systemic anaphylaxis) and inadvertent re-exposure is a risk, the patient should be advised to carry an Epi-Pen 1:1000 or Epi E-Z Pen (0.3 mg epinephrine) autoinjector (Center Lab, Port Washington, NY). If the patient is below 6 yr of age, an Epi-Pen Jr 1:2000 or Epi E-Z Pen Jr. (0.15 mg epinephrine) autoinjector is advised. In these cases, Medic Alert jewelry is also advised (*see* Chapter 5).

DIAGNOSIS AND MANAGEMENT OF SELECTED ALLERGIC AND ALLERGIC-LIKE DRUG REACTIONS

β-*Lactam Antibiotics*

In patients with a history of an allergic reaction to penicillin or other β-lactam antibiotics, penicillin skin testing should be done electively. Only 20% of adults and 10% of children with this diagnosis turn out to be actually allergic based on allergy skin testing (the positive penicillin allergy skin test rate is higher in the first year after a reaction). There are three reasons why the true allergy rates are low in individuals labeled allergic to penicillin.

1. In many cases, the original reaction, usually a rash is a result of an infection (usually viral) rather than the antibiotic used to treat that infection;
2. In cases of true penicillin allergy, the reaction rate dissipates about 10%/yr; and
3. In children, toxic (nonallergic) maculopapular rash to ampicillin/amoxicillin and to some cephalosporins, like Cefaclor™, are common (5% of antibiotic therapies).

In most cases, it is advisable to refer the suspected penicillin-allergic patient to an allergist/immunologist specialist for evaluation. Table 5 lists the penicillin skin tests based on commonly available agents. Penicilloyl polylysine is an example of the major breakdown product of penicillin drug metabolism coupled to a carrier protein. This test reagent is responsible for positive skin tests in patients presenting with an isolated skin rash (especially urticaria, or urticaria and angioedema). Penicillin G is the parent drug.

Table 5
Penicillin Skin Testing

Reagent	*Type of test*	*Dose*
Penicilloyl-polylsine (Pre-Pen)[a]	Prick/scratch/puncture	1 drop
test strength	Intradermal	0.02 mL
Penicillin-G, 10,000 U/mL[b]	Prick/scratch/puncture	1 drop
	Intradermal	0.02 mL
Penicillin—minor determinant mixture	Not commercially available in the United States	

[a]Schwartz Pharma, Kremers Urban Co., Milwaukee, WI.
[b]Serial dilutions (10, 100, 1000 U/L) advisable in very sensitive individuals.

A positive skin test to penicillin G correlates with all types of allergic reactions. A positive minor determinant mixture skin test (minor or secondary penicillin metabolites) (*see* Fig. 2) correlates best with more serious life-threatening, systemic anaphylaxis, penicillin reactions. Unfortunately, this latter skin test reagent is not available commercially, but is available in many allergist/immunologist offices.

The overall reliability of these skin tests (Pre-Pen plus Pen G) listed in Table 5 is approx 80%. The overall reliability of testing with these basic agents plus the minor determinant mixture is 96–99%. In the latter situation, if the skin test is negative, therefore, there is a 1–4% chance of a minor skin rash if the drug is given.

Penicillin skin testing also tests for other penicillin and cephalosporin antibiotics, since the penicillin skin test measures reactions to the β-lactam ring, which is common to all of these agents (*see* Fig. 1). Although the overall crossreactivity rate between penicillin allergy and cephalosporin allergy is only 6%, if the penicillin skin tests are positive, β-lactam antibiotics should be avoided, since any one individual is 100% at risk.

In cases where the skin test results are equivocal, a graded challenge with a single usual oral dose of the β-lactam antibiotic in question under controlled conditions followed by a 2+ h wait is advisable (*see* General Approach to Diagnosis and Management).

In cases where the individual is found to be allergic (history of reaction positive, confirmed by skin test and/or challenge), all β-lactam antibiotics should be avoided. Usually substitute medications are used to treat subsequent infections, particularly the sulfonamides, erythromycin, and clarithromycin (Biaxin™, Abbott Labs, North Chicago, IL).

In select cases where individuals who are proven β-lactam-antibiotic-allergic and need a β-lactam antibiotic (life-threatening or other serious infections without suitable substitutes available), then penicillin or the appropriate β-lactam antibiotic desensitization may be indicated. In these cases, it is advisable to consult an allergist/immunologist specialist.

Table 6 is an example of an oral penicillin desensitization protocol that can be used as a protocol for desensitization with penicillin and other β-lactam antibiotics. This procedure should only be done in the hospital under controlled conditions, such as an intensive care unit with a doctor present during the entire procedure. Each individual case is different, and published protocols are only guides to the procedure.

The oral route is believed to be safest, but the iv route may be preferable in some cases. Studies have shown that reactions during the procedure should be expected approx 30% of the time. When these occur, the patient should be treated appropriately and

Penicillin Allergy Skin Tests

- β-lactams are the only type of antimicrobial agents in which a suspected reaction (allergic) can be verified by skin tests (reliability up to 96–99%).
- Of those patients with a history of a prior reaction, only 20% of adults and 10% of children have been found to be skin-test-positive.
- Positive skin test to penicilloyl polylysine ("pre-pen") correlates best with urticarial reactions; Positive skin test to penicillin "minor determinant mix" correlates with anaphylaxis.
- Skin testing with penicillin G metabolites alone is a measure of potential clinical reactions to the β-lactam ring in amoxicillin and cephalosporins.

Table 6
Oral Penicillin Desensitization Protocol

Desensitization dose[a]	*Stock drug, 250 mg/5 mL concentration*	*Dose*[a] *given orally*	
		mL	*mg*
1	0.5 mg/mL	0.05	0.025
2		0.10	0.05
3		0.20	0.10
4		0.40	0.20
5		0.80	0.40
6	5.0 mg/mL	0.15	0.75
7		0.30	1.50
8		0.60	3.0
9		1.20	6.0
10		2.40	12.0
11	50 mg/mL	0.50	25
12		1.20	60
13		2.50	125
14		5.0	250

[a]Dose increased approximately every 20 min, unless reaction occurs. Then adjust accordingly.

stabilized before restarting the desensitization procedure. The next desensitizing dose should be less than the one producing the reaction.

Once the procedure is complete, the patient is usually maintained at a full treatment dose of the medication until the therapy is complete. Once the drug is stopped over 12–24 h, the patient should be considered to have reverted to his or her previous sensitized (allergic) state.

Sulfonamides and Other Antibiotics

Reactions to sulfonamides (particularly rashes) are common in the general US population. There is a marked accentuation of these rates in the patient with the HIV infection. In particular, with TMP-SMX, which is frequently used for the treatment and pro-

Drug Challenge and Desensitization

- Graded drug challenges, or drug desensitization, should be done only when necessary, with informed consent, and under controlled conditions by specialists familiar with these techniques
- Any serious (anaphylaxis or anaphylactoid) reactions following drug challenge usually start within 2 h of drug exposure
- Reactions during drug desensitization procedures, such as with β-lactam antibiotics, should be expected to occur in one-third patients.

phylaxis of *Pneumocystis carinii* pneumonitis, the reaction rates are as follows: general population 3%; immunodeficient patient (HIV sero-negative) 12%; AIDS (HIV sero-positive) 29–70%. Sulfa drugs are also likely to be associated with EM minor, SJS, and TEN types of reactions.

The allergic-like reaction to sulfonamides is not generally believed to be IgE-mediated or, for that matter, an immune event. Unfortunately, there is no skin test or no in vitro blood test to confirm a suspected reaction. In almost all cases, strict avoidance of the drug is recommended, once a presumptive diagnosis has been made.

The exception is life-threatening situations, such as in the patients with AIDS with *P. carinii* infection. In some cases, the infection can be successfully treated with other antimicrobial agents than the TMP-SMX, such as inhaled pentamidine. In other cases, this is not possible, and TMP-SMX is the optimal drug for treatment of active infection and/or use in *P. carinii* prophylaxis.

In some cases, adults with a documented history of a prior rash to TMP-SMX have later been given full doses of TMP-SMX without subsequent reaction. In other cases, serious reactions have resulted from this "full-dose" challenge.

Extended oral TMP-SMX desensitization procedures have proven successful in a limited series of patients: 10–23 d (19/21 patients); 10 d (23/28 patients); 2 d (6/7 patients). Use of "full-dose" challenge or desensitization is not advised for any patient who has a prior history of a drug-associated erythema multiforme, SJS, or TEN. The management of these situations is best left to the allergist/immunologist specialist.

Documented allergic-like reactions to other antibiotics are uncommon. Usually, they are not life-threatening in nature. Reactions to iv vancomycin result in a red flush ("red man syndrome") resulting from direct histamine release, and can be controlled symptomatically and with adjustment of the iv drug administration rate.

In the case of reactions to other antibiotics, in almost all situations long-term avoidance is usually recommended, and the event is documented in the patient's records. Since there are usually substitute antibiotics available, it is not a problem for most individuals.

In a few individuals, however, multiple antibiotic sensitivities of different types occur. This type of patient presents a problem when the primary care physician tries to treat common infections. In most cases, the β-lactam antibiotics are involved, so penicillin skin testing can be done. (Often, the tests are negative.) There are no convenient tests for reactions involving other antibiotics. Reproducible reactions of any kind, espe-

cially those that are systemic in nature, are rare. If this drug is implicated, a graded oral challenge followed by a 2-h wait in the office can usually be done without difficulty to prove the safety of this alternative antibiotic. (*See* General Approach to Diagnosis and Management.)

Insulin

Approximately 50% of humans given insulin regularly as a replacement therapy, especially the animal-derived forms, develop some IgE antibody to the insulin molecule that can be validated by a positive immediate reacting IgE skin test. Most of these individuals do not have clinical reactions to insulin. A few, however, do have bothersome local swelling at the insulin injection site.

Management of this local reaction problem consists of the following:

1. Division of the insulin dose in half and administering these at different sites;
2. Trial of an added oral antihistamine; and
3. If steps 1 and 2 fail, switching to another commercial type of insulin.

Generalized urticaria or systemic anaphylaxis to insulin is very uncommon (0.1–0.2% of diabetics). Usually the systemic reaction is the direct result of a diabetic discontinuing insulin replacement therapy regularly, for a period of time, and then resuming regular therapy. About 12 d after restarting the insulin, systemic anaphylaxis occurs.

Patients who have a systemic reaction to insulin should be hospitalized after first treating the acute symptoms. If the reaction is mild and the patient is seen within 24–48 h, the total insulin daily replacement can be decreased by one-third and subsequently, the dose can usually be safely increased 5 U/dose until therapeutic levels have been achieved.

In the situation where the reaction is more severe or the interval between reaction time and being seen is more than 48 h, the patient will require specific insulin allergy skin testing by an allergist/immunologist specialist in order to identify the least reactive insulin type (usually human insulin). The patient then requires desensitization over the course of a week with this new insulin.

Anesthetic Agents

Some patients given local anesthetics complain of allergic-like symptoms. Few, if any, of these reactions have been shown to be IgE-mediated. When confronted with such a problem, the goal is to find one local anesthetic that the patient can tolerate. The allergist/immunologist will usually skin test the individual complaining of symptoms with more than one type of local anesthetic, including the one that the surgeon/dentist wants to use.

The specialist will then select one of the nonreacting agents and then administer a graded sc injection challenge using dilutions of the local anesthetic at 1:100 (dose: 0.1 mL), 110 (dose: 0.1 mL), and full-strength local anesthetic (dose: 0.1, 0.5, 1.0, and 2.0 mL) at 15-min intervals, under controlled conditions.

Most patients successfully complete the local anesthetic challenge without difficulty. The referring physician is then informed regarding the safety of the drug used in the challenge.

During the induction of general anesthesia, it is common for an allergic-like reaction to occur (1:5000 to 1:15,000 inductions). The symptoms include urticaria, wheezing, rapid heart rate, low blood pressure, and shock. Two types of allergic reactions should be considered should these symptoms occur: (1) reactions to natural rubber latex and (2) allergic reactions to one of the neuromuscular blocking agents used in the induction period (e.g., tubocurarine chloride, alcuronium, gallamine triethiodide, pancuronium bromide, succinylcholine chloride, fluphenazine hydrochloride, thiopental, amytal sodium, and methohexital).

Certain individuals (e.g., health care workers, children with spina bifida or multiple surgeries, high allergic individuals, and individuals with atopic dermatitis), are at increased risk for systemic reactions to natural rubber latex. Usually, there is a history of a prior contact dermatitis or contact urticaria to latex products, before the patient reacts systemically. Latex proteins can be transferred via aerosol coupled to glove powder, so that severe reactions may occur in very sensitized individuals just by being in a room where latex is being used.

In situations where systemic anaphylaxis has occurred in an operating room, it is advisable to draw blood from the patient as soon as possible after the event so that in vitro testing can be subsequently performed for mast cell tryptase (as a sign of mast cell release—*see* General Approach to Diagnosis and Management) and IgE latex-specific antibodies. If the latex in vitro test is positive, it is diagnostic of this type of allergy. If the test is negative, the patient can be skin tested by most allergists/immunologists using a common latex rubber source (no commercial allergen for testing is available).

Although the allergist/immunologist specialist may attempt direct skin testing with various neuromuscular blocking agents, such a testing procedure is not standardized. Positive allergy skin testing to neuromuscular agents would provide helpful information, but a negative skin test result to these agents does not rule out an association between these agents and clinical reactions.

Aspirin (ASA) and NSAID

There is no skin test or in vitro test available to confirm the presumptive diagnosis of ASA/NSAID intolerance in patients who have a history of allergic-like reactions (e.g., urticaria or asthma). The only management is to advise the individual to avoid these drugs strictly. Although a graded drug challenge (beginning with no more than 3 or 30 mg of ASA, depending on the history of sensitivity, and advancing to 60, 100, 150, and 300 mg at 3-h intervals) has been studied experimentally, such a challenge is usually not advocated in most clinical situations. Also experimental is aspirin desensitization. Aspirin desensitization has proven successful in some patients with asthma, but not with rhinitis, polyps, or urticaria. This procedure is not recommended for the usually aspirin-sensitive asthmatic.

RCM

RCM is used in imaging diagnostic procedures, and adverse reactions to RCM are fairly common. Therefore, one allergic-like problem that a primary care physician is likely to face is the patient with a prior history of RCM reaction who needs another diagnostic imaging procedure.

Table 7
Pre-RCM Treatment Protocol for Prevention of Repeat RCM Anaphylactoid Reactions

Time	*Agent/dose*
18, 12, and 6 h before procedure	Prednisone 50 mg every 6 h for 3 doses (total 150 mg)
Immediately before procedure	Diphenhydramine hydrochloride (Benadryl™) 50 mg po, im, 1 h before **or** iv 5 min before RCM Cimetidine (Tagamet™) 300 mg or Ranitidine (Zantac™) 300 mg po, 1–3 h before, **or** iv 5 min before RCM
During procedure	Low-ionic RCM

There is no skin test or in vitro diagnostic test that can be done to predict whether or not the patient with a history of prior reaction to RCM will react again. Studies have shown that a patient who reacted before to conventional RCM will react again to the same material at a rate of approx 30%. This risk can be reduced to 10% by using a preprocedure treatment of prednisone and diphenhydramine (Benadryl™). It may be reduced to a risk of 0.5% by using a low-molarity RCM material plus a preprocedure treatment of medications as outline in Table 7.

In spite of these preprocedure treatments and the use of a low-ionic RCM during the procedure, the individual with a prior RCM reaction is at some risk, and the radiologist should be prepared to treat anaphylaxis should it occur (*see* Chapter 4). In addition to the usual treatments, the radiologist should be prepared to treat an unusual but occasionally severe RCM reaction that mimics excess vagal stimulation, inducing bradycardia and resistant shock. Under these special circumstances, the addition of atropine to the anaphylactoid treatment regiment may be lifesaving.

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17 β-Adrenergic Agonists

Clifton T. Furukawa, MD

CONTENTS

INTRODUCTION

β-adrenergic agonists and especially β-2 adrenergic agonists are generally prescribed for all asthmatics as a backup medication to anti-inflammatory therapy or, in the case of exercise-induced asthma, as the primary drug. Technological advances have led to the development of increased β-2-specific adrenergic agonists of longer duration of action. The effectiveness of β-adrenergic agonists in treating asthma is indisputable. However, the very effectiveness of these drugs causes problems of overuse and consequent side effects raising such issues as whether other drugs or other parameters should be preferentially utilized.

B-ADRENERGIC RECEPTORS

Initially, adrenergic receptors were classified as either α or β, based on the tissue response to various sympathomimetic amines. The receptor population that mediated excitatory responses was called α, and the potency ranking was epinephrine > norepinephrine > α-methyl norepinephrine > α-methyl epinephrine > isoproterenol. The receptor population that mediated inhibitory responses was designated as β, and had an agonist order of potency of isoproterenol > epinephrine > α-methyl epinephrine > α-ethyl norepinephrine > norepinephrine. It later became recognized that although generally correct, this classification was overly simplified, and the α and β receptors were further subclassified. For β-adrenergics, it is now recognized that there are three receptor groups, β-1, β-2, and β-3. The β-1 adrenergic receptors are primarily located

From: *Allergic Diseases: Diagnosis and Treatment*
Edited by P. Lieberman and J. Anderson Humana Press Inc., Totowa, NJ

in the lung and prostate, and the β-3 adrenergic receptors are found in brown and white adipose tissue. Improved techniques to identify receptors have led to the discovery that although these receptors have preferential primary locations, they may also be present in other tissues. The β-2 adrenergic receptor is the predominant β receptor in the lung, but is also found in adipose tissue, brain, heart, and placenta. This is of particular importance in understanding the side effects of the β-2-specific adrenergic drugs.

β-2 ADRENERGIC AGONISTS FOR THERAPY

Advances in therapeutic β-adrenergic agonists have been accomplished by modification of chemical structures of adrenergic agents (*see* Fig. 1). Although the specific chemical structure determines the specific class of drugs (e.g., catecholamines, noncatecholamines, saligenins), it may be more convenient to consider the available therapeutic agents as first-, second-, third-, and fourth-generation, depending on the newness of the drug, the β-2 specificity, and the duration of action.

First-Generation Agents (α and β)

Probably the oldest adrenergic drug is ephedrine, used in China as MaHuang for centuries before the use of epinephrine. Although ephedrine is rarely used for treatment today, it was commonly combined with theophylline and sometimes a sedative as treatment for asthma until more effective and more specific bronchodilators were developed. The major problem with ephedrine was that it easily crossed the blood–brain barrier and even modest doses had significant side effects, particularly headache. The amount of bronchodilation was also relatively weak.

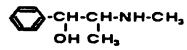
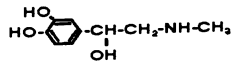
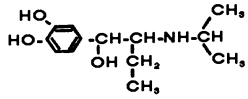
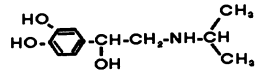
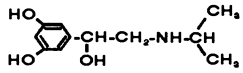
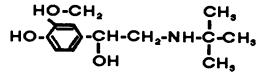
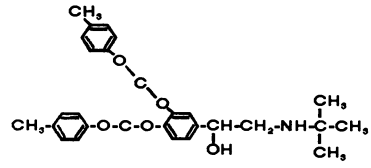
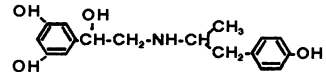
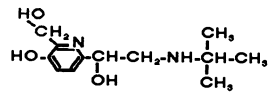
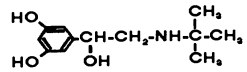
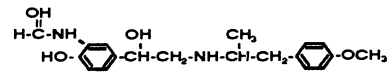
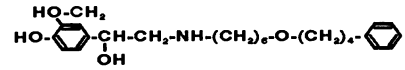
Epinephrine has both α- and β-adrenergic actions, which makes it the drug of choice for the treatment of anaphylaxis. It is effective as an injection, but not orally, because epinephrine and other catecholamines are rapidly inactivated by the action of catechol-o-methyltransferase (COMT), an enzyme present in the gastrointestinal wall. Epinephrine can also be aerosolized and is the active component of some over-the-counter asthma metered-dose inhaler preparations. Most physicians do not prescribe this type of bronchodilator, since other β-adrenergic agonists are more efficacious. Aerosolized epinephrine using a powered nebulizer is a popular treatment for acute laryngobronchitis (croup).

Second-Generation Agents (Relatively β)

Two other catecholamines are of note: isoproterenol and isoetharine. Isoproterenol is available for aerosol administration for asthma, but also is available for sublingual and injectable routes. As an inhaled bronchodilator, isoproterenol has good immediate potency, usually accomplishing peak bronchodilation within 5 min. However, the effectiveness rapidly declines and usually is lost completely by 2 h. This makes isoproterenol useful acutely, but not useful for any maintenance bronchodilator therapy, or even for prophylactic use before exercise. If high doses are used, cardiac stimulation becomes an unacceptable side effect.

Isoetharine is the first β agonist that clearly had increased β-2 activity. Because it also

Adrenergic Bronchodilators

Classification	Molecular Structure	Formulations in the USA	Duration of effect (h)
First Generation Ephedrine		Liquid, tablet	2-3
Epinephrine		Injection, MDI	<1
Second Generation Isoetharine		MDI, nebulizer solution	3
Isoproterenol		Injection, liquid, MDI, nebulizer solution, tablet	1-2
Metaproterenol		Liquid, MDI, nebulizer solution, tablet	3-5
Third Generation Albuterol		Dry powder inhaler, liquid, MDI, nebulizer solution, tablet	4-6
Bitolterol		MDI, nebulizer solution	6-8
Fenoterol		Not available	6-8
Pirbuterol		MDI	4-6
Terbutaline		Injection, MDI, tablet	4-6
Fourth Generation Formoterol		Not available	8-12
Salmeterol		MDI	12

MDI = metered dose inhaler

Modified from Kemp JP. Making best use of today's bronchodilators. J Respir Dis 1994;15 (4 suppl):S21-S27.

Fig. 1.

is a catecholamine, it cannot be used orally because of deactivation by COMT. It is, however, resistant to monoamine oxidase and so has a slightly longer duration of bronchodilation than the other catecholamines. Its clinical usefulness, however, has been greatly overshadowed by the more specific and longer-acting β-2 drugs.

Metaproterenol is a resorcinol, not a catecholamine. The resorcinol group has a modification in the 3,4 hydroxyl groups of the benzene ring. The hydroxyl groups repositioning from the 3,4 to the 3,5 positions makes metaproterenol resistant to inactivation by COMT, which leads to the advantage of prolonged duration of action. The side chain of metaproterenol is essentially the same as isoproterenol, so as would be expected, both drugs are similar in their effects relative to heart and lung. Since the relative cardiac effect is similar for both isoproterenol and metaproterenol, metaproterenol is less suited for maintenance bronchodilator treatment or for higher dose treatment than are the third generation of β-adrenergic agonists.

Third-Generation Agents (Highly β, Longer-Acting)

The third-generation group is those drugs that are highly β-2-specific with a longer duration of action. These characteristics make them the ideal choice for acute asthma treatment and prevention of exercise-induced asthma.

Albuterol, a saligenin, is resistant to the action of COMT because of the substitution of the 3 hydroxyl group with a hydroxymethyl group. In addition, albuterol has a tertiary butyl group that replaces the isopropyl group seen in isoproterenol and metaproterenol. This increased bulkiness of the side chain has resulted in substantially more selectivity for the β-2 receptor. Albuterol is resistant to degradation by COMT, making it effective orally as well as by aerosol and parenterally. With its high β-2 specificity and its longer duration of activity, albuterol became the standard against which other bronchodilators are compared.

Bitolterol is resistant to COMT because the 3,4 hydroxyl groups are esterified to form a di-*p*-toluate ester. This modification substantially prolongs the bronchodilator activity; in addition, a tertiary butyl group replaces the isopropyl group, resulting in increased β-2 specificity and protection of the drug against degradation by monoamine oxidase (which then further increases the duration of activity). Bitolterol is also an interesting bronchodilator because when administered by inhalation, it acts as a prodrug, which is slowly degraded to the active drug colterol. This gives bitolterol the potential of being much longer-acting than the other bronchodilators in this group.

Pirbuterol is resistant to COMT because of the substitution of a hydroxyl methyl group for the 3 hydroxyl group. This plus the increased size of the terminal amino group increases the duration of the bronchodilator action. The side chain is also adequately bulky to account for more selectivity for the β-2 receptor.

Terbutaline is resistant to COMT because of the repositioning of the hydroxyl groups to the 3,5 positions. This modification increases the duration of the bronchodilator action and makes the drug potentially capable of oral administration. The side chain of terbutaline has a tertiary butyl group that increases the β-2 specificity and also protects against degradation by monoamine oxidase, increasing the duration of bronchodilation. As with the other drugs in this third-generation group, terbutaline is of current useful-

Safety of β-Adrenergic Drugs when Used Appropriately

- Intermediate Action
  - Albuterol, terbutaline, pirbuterol, bitollerl—yes
  - Fenoterol[a]—No
- Long activity
  - Salmeterol—yes
  - Formoterol[a]—yes

[a]Not available in the United States.

ness, but it also has unique advantages as potentially the safest drug for use in pregnancy. It also is used by obstetricians to control premature labor.

Fenoterol is a drug that is not used in the United States, but has been part of substantial controversies about the safety of β agonists. Fenoterol, like other members of this group, is resistant to the action of COMT because hydroxyl groups are located at the 3,5 positions. The side chain in fenoterol is much larger than the other members of this group with the use of a 4-hydroxybenzyl moiety. Nonetheless, in the case of fenoterol, the β-2 specificity is less than those drugs that use a tertiary butyl group substitution. It is this relatively decreased β-2 specificity that makes fenoterol a drug that potentially could have more side effects than the other drugs in this group.

Fourth-Generation Agents (Highly β, Extremely Long-Acting)

Salmeterol and formoterol induce a long duration of bronchodilation, in some studies reported to be more than 12 h. These two drugs resemble the noncatecholamine-selective β-2 agents, but also possess bulky lipophilic side chains. It is thought that these side chains anchor the molecule next to the β receptor site. The action of both these drugs can be reversed by introducing a β-adrenergic blocking agent, but if the β-blocker is removed, the receptor is restimulated. Because of their long duration of action, these drugs are particularly useful for chronic bronchodilator treatment, but are potentially less useful acutely and may pose problems of toxicity with overuse or increased dosage. There are some interesting differences between salmeterol and formoterol. Formoterol, when given by inhalation, has a rapid onset of action, whereas salmeterol has a delayed onset of action even when given by inhalation. Formoterol, if given orally, has a duration of activity about equal to albuterol. When given by inhalation, it and salmeterol both have bronchodilation that persists at least 12 h. However, if the subgroup studied are consists of older nonsmoking asthmatics with some degree of fixed obstruction, formoterol activity can only be measured for up to 8 h. At present, formoterol is not available in the United States, and salmeterol is recommended for use under very specific guidelines. These include no more frequent use than two puffs two times a day, and warnings that it should not be initiated in patients with worsening or deteriorating asthma, should not be used for acute symptoms, and should not be considered a substitute for oral or inhaled corticosteroids. Thus, most experts recommend salmeterol use

concomitantly with inhaled anti-inflammatory therapy and availability of a shorter-acting inhaled bronchodilator for acute symptoms.

METHODS OF ADMINISTRATION

Oral

In general, oral dosing of β-adrenergic agonists requires larger administered doses than in other routes. Consequently, increased likelihood of side effects results. Of course, the only drugs useful orally are those that are resistant to COMT. However, variable absorption is also a concern owing to conjugation of the drug in the gut wall or presence of food in the stomach. Decreased bioavailability may result from rapid metabolism on first passage through the liver. In the case of terbutaline, this results in the bioavailability being only 7–26% when given by the oral route.

Sustained-release formulations have been particularly useful in nighttime asthma, but compared to sustained-release theophylline, may cause more side effects. Overall, the oral route of administration may only be useful for persons who are unable to use other routes of administration, such as very young children or elderly patients. However, nebulizer solutions can effectively be used by these patients.

Parenteral

Both terbutaline and albuterol have been used subcutaneously, by continuous iv infusion, and by bolus iv infusion. Such use has been primarily limited to hospitalized severe asthmatics, but continuing therapy has been reportedly used for up to several years. It is interesting that the principal side effect has been problems with sleeping and that tolerance did not occur.

Inhaled

Administration by inhalation is highly recommended, since drug effect is usually rapid and the dose required for adequate bronchodilation is usually accompanied by few side effects. It is interesting that when side effects do occur, they usually are of less duration than the duration of bronchodilation. Overall, the major reasons primarily to recommend inhalation rather than oral or injectable route of this class of drugs are that the effective dose and the side effects are less. In fact, many centers have as part of their protocol for dealing with severe hospitalized asthmatics the use of a continually nebulized selective β-2 bronchodilator as treatment prior to consideration of any more aggressive measures. This is particularly important in view of evidence that isoproterenol iv infusions have been shown to create myocardial injury.

There are, however, substantial problems in the use of the inhalation route if patients are not adequately trained in inhalation techniques. It is absolutely essential that all patients be taught how to use their inhaler or nebulizer and are given opportunity to demonstrate their competence at each followup evaluation. The use of spacers can also improve the efficiency of a metered dose inhaler, but with the increasing concern of fluorocarbon use, it is expected that self-actuated inhalers will be the standard. Devices, such as rotohalers, diskhalers, turbohalers, and so on, will make the use of spacers unnecessary.

ADVERSE EFFECTS

Tremor is a specific β-2 effect on skeletal muscles and thus is not separable from the bronchodilator action. However, tremor does decrease with continual use of β-adrenergic drugs. Side effects, such as increased heart rate and palpitations, are decreased with the more selectively β-2 drugs. However, since there are β-2 receptors in the myocardium, and since there is reflex sympathetic stimulation of the heart as a consequence of β-2 relaxation of the vasculature that supports skeletal muscles, there is always some degree of increased heart rate and cardiac output if the dosage of the β-2 drug is high enough. With long-term use, hyperglycemia and hypokalemia may result. Hypokalemia does occur from direct stimulation of the sodium-potassium pump in the cell membrane, and so can occur acutely. Further hypokalemia occurs with steroid or diuretic treatment, so that a hypoxemic patient could experience arrhythmias.

Since the 1960s, this class of drugs has been implicated as contributory to asthma deaths. In the 1960s, asthma mortality was increased in the United Kingdom at the same time that high-dose isoproterenol metered dose inhaler sales increased. When these devices were made prescription and subsequent sales were decreased, there was a decline in the number of asthma deaths. In the mid-1970s, New Zealand noted a sharp increase in asthma deaths at the same time that fenoterol as a metered dose inhaler went into increased use in this population. In the last few years, studies of pharmacy use and morbidity and mortality in Canada implicated fenoterol and albuterol overuse in death and near deaths from asthma. However, other studies and a meta-analysis of case-control studies noted that the relationship between β-agonist use and death from asthma is a weak one. More important may be overuse of medication in patients who are not adequately managing their disease. Consequently, comprehensive overall management of the patient's disease has been emphasized as the most effective way of minimizing potential adverse effects from his or her medications. Thus, the emphasis on treatment being primarily directed toward the prevention and treatment of inflammation is appropriate. Except for use in preventing exercise-induced asthma, any use of this class of bronchodilators beyond three times/24 h should be considered reason for re-evaluation of the asthmatic's management program.

US OLYMPIC COMMITTEE DRUG RULES

At present, this class of drugs falls under stimulants, so the US Olympic Committee has banned certain forms of β-2 agonists. Currently permitted β-2 agents are albuterol, terbutaline, and salmeterol. These are permitted by inhalation only, and only with written notification from the prescribing physician sent prior to competition indicating its appropriateness of use because of exercise-induced asthma or for asthma. All adrenergic medications by any oral or injectable route are banned, and β-2 agents other than albuterol, and salmeterol are banned even if given by inhalation. The basic reason for this is that some of the β-2 agents possess anabolic properties, particularly if they are taken orally or given by injection. The allowable list of medications is constantly being reviewed by the committee and constantly revised and changed, so that this information should be checked regarding currency on a regular basis.

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18 Theophylline

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CONTENTS

INTRODUCTION

Theophylline was introduced into clinical medicine almost 50 years ago for the treatment of asthma. The drug was widely used for 20 years after its introduction; however, following reports of adverse reactions, including death, there was a pronounced decline of theophylline prescribing, particularly for children. In the mid-1960s and the early 1970s when the pharmacokinetics of the drug began to be elucidated, an increase in the use of theophylline occurred, and it became the most commonly prescribed drug for the treatment of asthma. This trend is now being reversed; doubts are being raised even about its bronchodilator activity in certain clinical settings, e.g., acute asthma. Furthermore, concurrent with its increased use, theophylline toxicity, which was well characterized in the 1950s and 1960s, was rediscovered, dampening enthusiasm for the drug.

Theophylline is a methylated xanthine, closely related to naturally occurring caffeine and theobromine. A theophylline derivative, dihydroxypropyl theophylline (dyphylline) marketed as Lufyllin® and Dilor®, is promoted as being safer than theophylline because it is eliminated principally through the kidneys, and its disposition is unaffected by the multiple factors that influence the biotransformation of theophylline in the liver. Unfortunately, dyphylline has substantially less bronchodilator activity than theophylline, and because of its water solubility, dyphylline is rapidly excreted from the body with an elimination half-life of approx 2 h.

From: *Allergic Diseases: Diagnosis and Treatment*
Edited by P. Lieberman and J. Anderson Humana Press Inc., Totowa, NJ

MECHANISM OF ACTION

Xanthines are known to relax airway and other smooth muscles; however, the degree of relaxation of airway smooth muscle is less than that achieved with inhaled adrenergic agents in acute bronchoconstriction. Studies suggest that the bronchodilator, anti-allergic, and anti-inflammatory effects of xanthines occur through multiple molecular mechanisms of action. Theophylline has a variety of effects, including antagonism of prostaglandins, effects on intracellular calcium flux, and the property of causing increased binding of 3′,5′-cyclic adenosine monophosphate (cAMP) to 3′,5′-cAMP binding protein. Binding to adenosine receptors in the brain explains theophylline's potential to cause seizures, but not its bronchodilator activity. Bronchodilator activity, based on annual studies, appears to be mediated by theophylline inhibition of two phosphodiesterase isoenzymes, PDE III and PDE IV.

Evidence, both from animal studies and in humans, has suggested that in addition to its bronchodilator properties, theophylline also possesses some anti-inflammatory and/or immunomodulatory activity. In studies that provide evidence for anti-inflammatory action of theophylline, investigators have reported attenuation of response to nonspecific agents used in airway challenge studies in asthma, such as methacholine, carbachol, histamine, and hypotonic saline. Immunomodulatory effects have been suggested by changes in lymphocyte population. Theophylline also causes a serum concentration-dependent protection against exercise challenge in asthmatic patients. Response to exercise and airway reactivity are closely linked. Alternatively, in similar studies, other authors have not found any evidence of an anti-inflammatory effect of theophylline as reflected in decreased bronchial responses to the same agents and in prevention of an allergen-induced increase in airway reactivity. Thus, although the majority of studies provide evidence of anti-inflammatory activity, the issue is still clouded. Theophylline also has some extrapulmonary effects that may be of clinical relevance. These include increased myocardial and diaphragmatic contractibility and delay in onset of respiratory muscle fatigue.

PHARMACOKINETICS

Absorption

Rapid-Release Formulations

Theophylline is rapidly absorbed from orally and rectally administered formulations and from orally administered uncoated tablets or liquid preparations. The speed, but not the extent, of absorption is affected to a clinically insignificant degree by concurrent ingestion of food or antacid. For iv use, aminophylline continues to be the preferred product. The dose administered needs to be corrected for the fact that aminophylline is 80–85% theophylline.

Slow-Release Formulations

Slow-release theophylline formulations are indicated for patients in whom elimination half-lives are <6 h and for enhancing compliance, because less frequent dosing is required. Various products differ in terms of rate and extent of absorption. The ideal product releases the drug at a constant rate over the dosing interval. Slow-release for-

mulations vary in the rate of the drug released (from slow to slower to ultraslow). With the ultraslow products, the rate of drug release is typically so slow that the drug may be out of the gut before it is completely absorbed. There is diurnal variation in theophylline absorption, which results in higher morning trough concentrations. It has been proposed that host factors, in addition to the drug itself, are responsible for some of the erratic absorption patterns. To minimize fluctuation in serum concentration over a dosing interval, the patient's theophylline elimination characteristics (slow or fast) should ideally be matched to the product's release characteristics (slow, slower, or ultraslow). Most children over the age of 6–8 yr can be successfully treated with 12-h dosing intervals with some slow-release preparations (e.g., Slo-bid Gyrocaps, Uniphyl, Theo-Dur, or Uni-Dur Tablets). Patients with exceptionally rapid theophylline clearance require 8-h dosing intervals to prevent serum concentration fluctuation >100%. On the other hand, individuals, e.g., the elderly, who eliminate theophylline very slowly will maintain therapeutic levels of theophylline with once-a-day dosing of most extended-release products. Food taken concurrently with theophylline has an important effect on the rate of drug release with some products and minimal or no effect with others. Once-a-day products are more vulnerable to variations in intestinal pH and mobility. The best example of the food effect on slow-release theophylline absorption has been reported with Theo-24. When given with a high-fat-content meal (50% carbohydrate, 20% protein, and 30% fat), about half of the dose of Theo-24 is absorbed in a 4-h period (usually beginning 6–8 h after ingestion), and peak concentrations average two to three times higher than those observed when this drug was given during fasting. This phenomenon of "dose dumping" (defined as more than 50% of the total dose being absorbed in <2 h) is a particular hazard with once-a-day products, in which the total dose is given at one time. Antacids may affect the rate of drug absorption from products with pH-dependent dissolution in contrast to absorption of formulations whose dissolution is not pH-dependent (e.g., Slo-bid Gyrocaps, Theo-Dur Tablets).

DISTRIBUTION

The pharmacokinetics of theophylline can be characterized by the use of a linear, two-compartment open model, because the multicompartment characteristics of theophylline are not very pronounced. After iv administration, theophylline distributes rapidly from the plasma to its site of action in the tissues; this distributive phase is virtually complete within 30 min. The volume of distribution averages about 0.45 L/kg in children and adults (within reasonable parameters of ideal body weight). Theophylline also passes through the placenta and into breast milk and crosses the blood–brain barrier. Concentrations in the central nervous system (CNS) in children are about 50% of the serum concentration (90% in premature infants). Salivary concentrations are approx 60% of serum levels.

METABOLISM

Theophylline is eliminated from the body principally by biotransformation in the liver to inactive (with the exception of 3-methylxanthine) metabolites. The enzymes responsible for the metabolism of theophylline (and many other drugs) belong to the cytochrome P-450 family of oxidases located in the smooth endoplastic reticulum of the

liver. Theophylline metabolism is age-dependent. In infants, drug biotransformation is slow as a result of immaturity of hepatic microsomal enzymes and slowly increases during the first year of life. By 8–12 mo of age, clearance rates approach those seen in early childhood. From 1–9 yr of age, the rate of theophylline metabolism accelerates. There is a gradual decline in the rate of theophylline biotransformation during the adolescent and early adult years. At about 16 yr of age, the metabolic rate approximates that seen in young adults. After 1 yr of age, approx 10% of the drug is excreted unchanged in the urine. In premature infants and normal newborns during the first month of life, 45–50% of an administered dose of theophylline is cleared by the kidney unaltered. At all ages, a small amount (approx 6%) of theophylline is *N*-methylated to caffeine. This minor conversion becomes clinically relevant only in premature infants, in whom caffeine has an extremely long half-life (mean, 96 h), which results in its accumulation and pharmacologic effect.

Because liver microsomal enzyme activity is not only dependent on age, but also subject to the inducing and inhibiting action of a large variety of unrelated environmental conditions and disease factors, it is not surprising that there is an intraindividual variation over time in the rate of metabolism of theophylline and resultant serum concentration. Individual variations in theophylline metabolism, however, are small, unless there are changes in disease factors (e.g., fluctuating cardiac function) or changes in concurrent drug therapy. Other factors affecting theophylline clearance include cigaret smoking, marijuana smoking, and, to a small extent, diet. There is a dose-related increase in theophylline clearance; heavy smokers metabolize theophylline twice as fast as nonsmokers. Smokers of marijuana also have accelerated theophylline metabolism. Ingestion of a high-protein, low-carbohydrate diet accelerates theophylline metabolism, presumably by increasing liver enzyme activity. Dietary intake of methylxanthines, caffeine in particular, affects theophylline metabolism by acting as a competitive substrate for theophylline-metabolizing enzymes. The ingestion of charcoal-broiled meat, presumably because of a stimulating effect on liver enzyme function of polycyclic hydrocarbons produced during the charcoaling process, has been reported to increase metabolism of theophylline. Although of theoretical intent, dietary factors are seldom a clinically significant problem. Although the data are conflicting, the effect of obesity on theophylline clearance appears to be negligible. Because theophylline distributes poorly into fat, dosage should be based on ideal body weight rather than actual weight.

Theophylline metabolism is affected by various disease states, including hepatic disease, cardiac disease, and viral illnesses. Hepatic dysfunction is a major cause of altered theophylline biotransformation. Patients with decompensated cirrhosis, acute hepatitis, and possibly cholestasis have reduced theophylline clearance. A correlation between slow hepatic metabolism and serum albumin and bilirubin concentration has been made in patients with cirrhosis. Cardiac disease, presumably causing decreased liver microsomal enzyme function by passive congestion of the liver secondary to congestive heart failure, may have a profound effect on theophylline metabolism. When heart failure is treated, theophylline clearance increases. Acute viral illnesses, especially influenza, associated with fever have been reported to prolong theophylline half-life. Symptoms of nausea, vomiting, and headache are commonly observed in children during many viral infections; however, when these symptoms develop in a child receiving theophylline, the physician must consider the possibility of theophylline intoxication. If fever is high

Table 1
Factors Other than Drugs
That Influence Theophylline Clearance

Factors	*Decreased clearance*	*Increased clearance*
Age	Premature infants; neonates and up to 6 m; adults over 60 yr	Ages 1–16 yr
Diet	Dietary methylxanthines	—
Habits	—	Cigaret smoking (tobacco or marijuana)
Disease	Liver disease, hypothyroidism, congestive heart failure, acute pulmonary edema, chronic obstructive pulmonary disease, sustained fever usually with viral illness	—

and sustained (e.g., higher than 102°F for more than 24 h), the dosage should be reduced in a patient whose theophylline serum concentration was previously maintained within the therapeutic range (*see* Table 1).

Drug interactions are another factor in altering theophylline elimination. The most important drug interaction is the effect of cimetidine in decreasing theophylline clearance. The macrolide group of antibiotics may also have a similar effect on theophylline biotransformation. The degree of effect differs among agents in this class of drugs. Troleandomycin has the most profound effect, followed by erythromycin estolate. Phenytoin and rifampin, drugs known for their P-450 enzyme-inducing properties, appear to accelerate theophylline metabolism. The effect of phenobarbital is variable; some studies have shown no effect and others have revealed a stimulatory effect on theophylline metabolism, especially when phenobarbital, in doses producing therapeutic serum concentrations, is given for 4 wk or longer (Table 2).

THERAPEUTIC DRUG MONITORING

The rationale for therapeutic monitoring of theophylline serum concentration is that it is a major determinant of both efficacy and toxicity. Theophylline has a narrow therapeutic index, which makes it imperative for the physician to understand that serum concentration may be affected by many factors that affect liver microsomal enzyme function and alter elimination kinetics.

During the treatment of an acute exacerbation of asthma, a serum theophylline level should be drawn before administration of an iv loading dose of aminophylline if the patient has been receiving theophylline. In this circumstance, the initial bolus may need to be reduced by 25–50%, depending on the result. For a patient who is admitted to the hospital and receives a constant infusion of theophylline after the bolus, it is important to obtain a 1-h level and adjust the serum concentration to the therapeutic range. Thereafter, serum theophylline levels should be monitored every 12–24 h.

Table 2
Clinically Important Drug Interactions with Theophylline

Decreases theophylline metabolism resulting in increase in serum concentration	*Increases theophylline metabolism resulting in decrease in serum concentration*
Allopurinol	Aminoglutethimide
Cimetidine	Carbamazepine
Ciprofloxacin	Phenobarbital (PB)
Clarithromycin	Phenytoin
Disulfiram	Rifampin
Mexiletine	Sulfinpyrazone
Propanolol	
Enoxacin	
Erythromycin	
Estrogen	
Fluvoxamine	
Interferon, human recombinant α-A	
Tacrine	
Thiabendazole	
Troleandomycin	

The indications for monitoring theophylline serum concentrations and management of chronic asthma are subject to some controversy. Some authors believe that all patients with chronic asthma should be monitored at regular intervals during the initial phase of theophylline adjustment. These intervals vary, and it is assumed that theophylline clearance is stable. Other clinicians reserve monitoring for patients who do not obtain optimal symptom control after an appropriate dose is given and for patients in whom adverse effects develop. In the event of symptoms associated with theophylline toxicity, immediate determination of serum theophylline concentration is mandatory. To interpret serum theophylline concentration properly in clinical situations, a significant amount of information must be provided with a sample, such as characteristics of the patient (age, weight), formulation of the drug (rapid release or slow release), dosage, duration of therapy (to ensure steady state for maintenance-dose adjustment), dosing interval, exact timing of previous adjustment, exact timing of blood collection, concurrent drug therapy, and presence of fever or other disease states, such as congestive heart failure or liver dysfunction. With a rapid-release theophylline product (liquid or tablet), a sample obtained 2 h after the dose approximates the peak concentration. The determination of the trough concentration (the sample obtained immediately before the next dose) does not provide much additional information except to show the magnitude of the peak–trough difference. Because of a circadian effect on theophylline absorption, specimens should be drawn during the same dosing interval when more than one measurement is being compared. Various slow-release products differ in their release characteristics (e.g., Theo-Dur Tablets or Slo-bid Gyrocaps reach peak serum concentration approx 3–7 h after the morning dose). Slow-release products that have pH-dependent dissolution characteristics (e.g., Theolair and Theo-24) release drugs at variable rates,

Possible Beneficial Effects of Theophylline

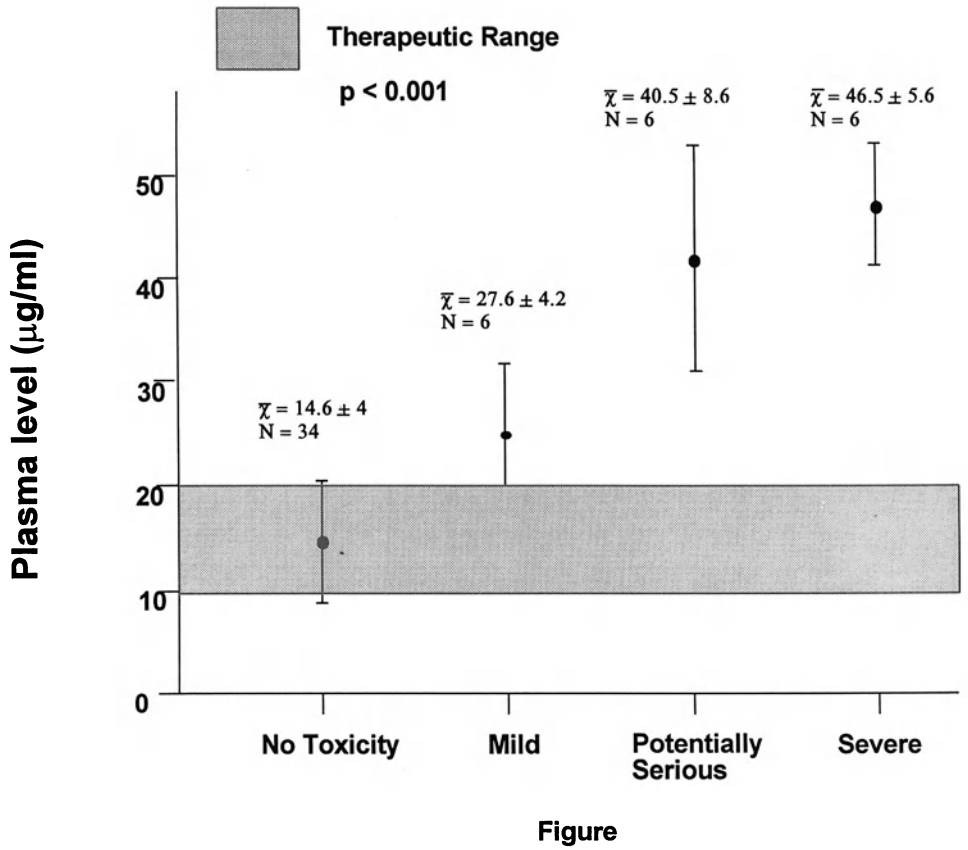
- Bronchodilatation seems to be its major activity. This is mediated through the inhibition of phosphodiesterase enzymes.
- Theophylline also may have anti-inflammatory and/or immunomodulatory activity via its actions on eosinophils and lymphocytes.
- Theophylline also exerts a beneficial effect on respiratory muscle fatigability and diaphragmatic contractility.

- There is a linear relationship between the log of serum theophylline concentrations and improvements in FEV_1 between theophylline concentrations of 5–20 μg/mL.
- The therapeutic window is relatively small, and toxic symptoms occur when this therapeutic window is exceeded; therefore, monitoring is often necessary.
- Multiple factors affect theophylline metabolism and, therefore, serum theophylline levels. These include age, smoking habits, other drugs, and so forth.
- Each theophylline preparation has its own characteristics of absorption, and the physician must be familiar with the preparation utilized.

depending on whether they are given during fasting or with a meal. Intersubject and intrasubject variability in absorption of slow-release products may be the reason for a theophylline serum level to be inconsistent or lower than the expected level for a particular dose. An important reason for inconsistent levels of theophylline is poor patient compliance.

PHARMACODYNAMICS

It is well recognized that there is a linear relationship between the logarithm of serum theophylline concentration and improvement in forced expiratory volume in 1 s (FEV_1). This relationship was first shown in children by Maselli and colleagues, who showed a strong correlation between the intensity of bronchodilator effect (improvement in FEV_1) and the logarithm of the amount of drug in the tissue compartment. It was evident from this study that the effect on pulmonary function was not seen until 30 min after the bolus injection of iv aminophylline; this lag represented the time for the drug to be distributed from the plasma to the site of action in the tissues. Because the bronchodilator effect increases and then falls rapidly after a bolus, it is logical to give iv aminophylline by constant infusion rather than by repeated bolus injection after the initial bolus dose. Mitenko and Ogilvie also studied the log serum concentration–bronchodilator relationship in a group of hospitalized adult asthmatic patients and showed a proportionality between the log of the serum concentration and the bronchodilator effect over the 5–20 μg/mL range. Subjects with severe asthma (status asthmaticus) have a rather flat serum concentration–bronchodilator effect curve over the range of 5–20 μg/mL. In patients with mild asthma who may have a nearly normal FEV_1 of 50–60% of the predicted level, the serum concentration–response curve is steep.



Figure

Fig. 1. Frequent toxicity from IV aminophylline infusions in critically ill patients. Modified from Hendeles L, Bighley L, Richardson RH, et al. *Drug Intell Clin Pharm* 1977; 11: 12–18.

THEOPHYLLINE TOXICITY

Like its bronchodilator activity, adverse effects are related to the logarithm of the serum concentration. Hendeles and associates demonstrated a relationship between serum concentration and symptoms of theophylline toxicity. Few toxic symptoms were noted when the steady-state serum concentration was <14.6 μg/mL. Adverse effects appeared as the serum concentration rose beyond 20 μg/mL. These included gastrointestinal, CNS, and cardiovascular effects (Fig. 1). Of all adverse effects, those involving the gastrointestinal tract are most common. Vomiting, particularly if persistent, is very suggestive of theophylline toxicity. Hematemesis has been reported primarily in children; its exact pathogenesis is not clear. Gastrointestinal symptoms occur most often as a result of a central effect of an excessive serum theophylline concentration on the medulla rather than because of a local irritative effect on the stomach. Relaxation of cardioesophageal smooth muscle may lead to gastroesophageal reflux and worsening of asthma by reflex stimulation of neural receptors in the distal esophagus, or by aspiration of stomach contents into the upper airway and lung.

Theophylline stimulates the nervous system at various levels: the medulla (increased respiratory rate and sensitivity to carbon dioxide nausea and vomiting), vagal effect (causing bradycardia), the cerebral cortex (restlessness, agitation, tremor, irritability, headache, seizures, difficulty in concentration, behavioral disturbances), the hypothalamus (hyperthermia), and even the spinal cord (hyperreflexia). The mechanism of theophylline's effect on the nervous system is not known. Although seizures are a prominent manifestation of theophylline toxicity and are often difficult to control, they themselves do not necessarily lead to death or to irreversible brain damage. Serum concentration associated with seizure activity varies substantially. The combination of seizures and cardiorespiratory arrest leads to the most disastrous consequences of theophylline intoxication. Individuals who are resuscitated and survive show signs of severe anoxic brain injury, much like those who have been resuscitated after drowning or strangulation. Theophylline may cause behavioral disturbances in children treated with the drug. In some instances, these effects appear to be related to dose and serum concentration, and in others, no such relationship exists. Concern about the effects of theophylline on behavior, particularly learning, was raised by Rachelefsky and coworkers; however, there were many commentaries and critiques of this study. Furukawa and associates, in two studies of theophylline in asthmatic children, also interpreted their results to suggest that theophylline may impair learning and behavior. It is of interest that one important abnormal finding in their initial report was not substantiated in their second study. Creer and McLoughlin, after a critical review of the subject, commented that there is no definitive evidence that theophylline produces any type of learning disability. A similar conclusion was reached by the US Food and Drug Administration Pulmonary/Allergy Drug Advisory Committee in 1987 after a review of studies published until that time. The elderly appear to be more sensitive to the effects of theophylline after chronic overdosing than do younger adults.

Theophylline has both inotropic and chronotropic effects on the heart. Although a number of opposing factors (direct effect on pacemaker tissue, effect on catecholamine release, peripheral vagolytic action, stimulation of the medullary center) confound the effects of theophylline on heart rate, the net result is usually tachycardia. In the therapeutic range, the effect of theophylline on the heart rate is modest, in the range of 3–16 beats/min. On the other hand, tachycardia is an almost constant finding in cases of significant theophylline intoxication. The arrhythmogenic potential of theophylline has been shown in experimental animals, but data in humans are less clear. Metabolic effects, principally hypokalemia and hyperglycemia, are commonly observed in cases of severe theophylline toxicity.

The appropriate treatment of theophylline toxicity is based on history, clinical signs and symptoms, and theophylline serum concentration determinations. For patients with acute overdose and serum concentrations in the 20–30 μg/mL range, administration of oral-activated charcoal 0.5 g/kg up to 20 g and monitoring of serum theophylline concentration for 2–4 h after the dose are often all that is needed. In acute overdose situations with serum concentrations between 30 and 100 μg/mL administration of multiple doses of oral activated charcoal as indicated above given every 2 h with serum theophylline concentration monitoring is appropriate. Since patients with theophylline toxicity are almost invariably vomiting, administration of the charcoal must often be via a

nasogastric tube. If the oral activated charcoal therapy is ineffective and serum theophylline continues to rise, serious consideration should be given to institution of charcoal hemoperfusion if the facilities are available. In an acute overdose situation with serum concentrations of >100 μg/mL, prophylactic anticonvulsive therapy should be considered in addition to multiple-dose administration of activated charcoal. If signs and symptoms of CNS irritation are such that a seizure is anticipated, anticonvulsive therapy should be initiated with an iv dose of abenzodiazepine (e.g., diazepam in a dose of 0.1–0.2 mg/kg every 1–3 min until seizure is terminated). If seizure control is not obtained, then a loading dose of phenobarbital 20 mg/kg should be infused over 30–60 min. Of course, monitoring of vital signs and electrocardiogram (ECG) should be instituted in all cases of significant theophylline toxicity. Recommendations for treatment of theophylline toxicity occurring in patients as a result of chronic overdosage are similar to those for acute overdosage with the following caveat. Young patients tolerate acute overdosage much better than the older patients, who most often are suffering from chronic overdosage. Serious adverse events are more likely to occur at lower serum concentrations in the chronic overdose situation, and therefore, more aggressive measures are indicated in this setting. In patients older than 60 yr of age, seizures may occur at levels lower than 30 μg/mL and therefore, prophylactic anticonvulsive therapy should be instituted earlier than in the young individual suffering from acute theophylline overdosage. Communication with a poison control center should be sought in cases of serious theophylline concentration.

Clinical Use of Theophylline in Asthma

Although iv aminophylline has been standard treatment for status asthmaticus since the early 1940s, the value of aminophylline in the emergency room setting for acute asthma has been questioned recently. Various authors have suggested that theophylline adds little in terms of bronchodilator activity while increasing adverse effects when optimal therapy with aerosolized β_2 agonists has been given. In an early study of the use of iv theophylline in the treatment of acute asthma, theophylline was compared with sc epinephrine in an emergency department. The bronchodilator effect of theophylline was inferior to that achieved by the epinephrine. Subsequent studies have generally confirmed the observation that in acute asthma, the bronchodilator effect of aminophylline is inferior to that of optimal administration of aerosolized β agonists. However, published data support the addition of iv aminophylline in the treatment of patients who fail optimal aerosolized β agonist therapy and who require hospital admission. For example, Pierson and associates showed clinical benefit and pulmonary function improvement in status asthmaticus in a double-blind study of iv aminophylline in children with status asthmaticus. An emergency department study of adults with acute airway obstructive disease showed a threefold decrease in hospital admission rates for subjects treated with aminophylline in comparison with placebo recipients. Sakamoto and colleagues reported on results of a study of iv aminophylline administration in 12 asthmatic patients with acute episodes varying from mild or moderate to severe. They found progressive improvement in FEV_1 over the range of 5–15 μg/mL; the greatest bronchodilator effect was observed in patients whose initial airway obstruction was of a milder degree. Extrapulmonary effects of theophylline in both improving diaphragmatic function and delaying the onset of muscle fatigue are a useful additional benefit

of theophylline administration. For iv therapy with aminophylline, some simple calculations can be used to determine the correct loading and maintenance therapy doses. In the case of drugs, like theophylline, that are distributed rapidly from the plasma to the tissues, there is a relationship among plasma concentration (C_p), dose (D), and volume of distribution (V_d) so that

$$C_p = D/V_d \quad (1)$$

If an average V_d of 0.5 L/kg is assumed, it is easy to determine that for each mg/kg (ideal body wt) infused, there will be an increase of approx 2 mg/L (2 μg/mL) in peak plasma concentration. The loading dose (aminophylline) needed to achieve a given theophylline plasma concentration is determined as follows (in the following equations 0.8 is used in the denominator to correct for the fact that aminophylline is 80% theophylline):

$$\textit{Loading dose } (D) = (V_d)\ [\textit{desired plasma concentration } (C_p)]/0.8 \quad (2)$$

In this equation, it is assumed that the patient has not previously been receiving theophylline. If theophylline has been taken on an outpatient basis, the loading dose should be reduced, unless an immediate serum theophylline determination is available. Once the observed level of theophylline is known, it can be subtracted from the desired level and multiplied by the volume of distribution:

$$D = V_d\ (C_p\ \textit{desired} - C_p\ \textit{initial})/0.8 \quad (3)$$

The dose of aminophylline required in order to maintain a desired steady state of serum theophylline concentration (C_{pss}) may be calculated as follows:

$$\textit{Constant infusion rate} = (Cl)\ (C_{pss})\ (\tau)/0.8 \quad (4)$$

where Cl is the clearance L/h/kg, C_{pss} is the average plasma concentration at steady state, and τ is the dosing interval. A theophylline level determined from a serum sample obtained 1 h after the loading dose is useful in determining the need for an additional bolus loading dose. Therefore, Eq. (1) can be used to calculate the subsequent loading dose if needed. A subsequent determination 4 h after the initiation of a constant infusion shows the trend of the serum concentration; the rate can either be increased or decreased as needed. Additional samples after 12 and 24 h guide further iv dosing.

To convert the iv dose to an equivalent oral dose, the hourly dose is multiplied by the dosing interval to be used for oral therapy. It is important to correct the aminophylline dose to obtain the theophylline equivalent by multiplying the aminophylline dose by 0.8. In this calculation, it is assumed that the oral product is completely absorbed.

When theophylline is used for the management of chronic asthma, it is most effectively administered as one of the sustained-release formulations. Use of sustained-release products minimizes the peak-and-trough fluctuation of serum concentration. Depending on an individual's serum theophylline clearance, an 8- or 12-h, or even 24-h dosing interval is appropriate. In general, the younger the child (under 9 yr of age), the more likely it is that an 8-h dosing interval will be required to minimize peak-and-trough fluctuations in theophylline concentration. Determination of theophylline serum concentration during the initial weeks of treatment is useful in adjusting the dose and dosing interval. Sustained-release theophylline products that are completely absorbed

Table 3
Dosing Titration (as Anhydrous Theophylline)[a,b,c]

Infants < 1 yr old
Initial dosage
Premature neonates
<24 d postnatal age; 1.0 mg/kg every 12 h
≥24 d postnatal age; 1.5 mg/kg every 12 h
Full-term infants and infants up to 52 wk of age
Total daily dose (mg) = [(0.2 × age in weeks) + 5.0] × (kg body wt)
Up to age 26 wk; divide dose into three equal amounts administered at 8-h intervals
>26 wk of age; divide dose into four equal amounts administered at 6-h intervals
Final dosage
Adjusted to maintain a peak steady-state serum theophylline concentration of 5–10 μg/mL in neonates and 10–15 μg/mL in older infants. Since the time required to reach steady state is a function of theophylline half-life, up to 5 d may be required to achieve steady state in a premature neonate, whereas only 2–3 d may be required in a 6-mo-old infant without other risk factors for impaired clearance in the absence of a loading dose. If a serum theophylline concentration is obtained before steady state is achieved, the maintenance dose should not be increased, even if the serum theophylline concentration is <10 μg/mL

Children (1–15 yr) and adults (16–60 yr) without risk factors for impaired clearance

Titration step	*Children < 45 kg*	*Children > 45 kg and adults*
Starting dosage:	12–14 mg/kg/d up to a maximum of 300 mg/d divided every 4–6 h	300 mg/d divided every 6–8 h
After 3 d, if tolerated, increase dose to:	16 mg/kg/d up to a maximum of 400 mg/d divided every 4–6 h	400 mg/d divided every 6–8 h
After 3 more days, if tolerated, increase dose to:	20 mg/kg/d up to a maximum of 600 mg/d divided every 4–6 h	600 mg/d divided every 6–8 h

Patients with risk factors for impaired clearance, the elderly (>60 yr), and those in whom it is not feasible to monitor serum theophylline concentrations
In children 1–15 yr of age, the initial theophylline dose should not exceed 16 mg/kg/d up to a maximum of 400 mg/d in the presence of risk factors for reduced theophylline clearance or if it is not feasible to monitor serum theophylline concentrations. In adolescents ≥ 16 yr and adults, including the elderly, the initial theophylline dose should not exceed 400 mg/d in the presence of risk factors for reduced theophylline clearance or if it is not feasible to monitor serum theophylline concentrations.

Loading dose for acute bronchodilatation:
An inhaled β-2 selective agonist, alone or in combination with a systemically administered corticosteroid, is the most effective treatment for acute exacerbations of reversible airways obstruction. Theophylline is a relatively weak bronchodilator, is less effective than an inhaled β-2 selective agonist, and provides no added benefit in the treatment of acute bronchospasm. If an inhaled or parenteral β agonist is not available, a loading dose of an oral immediate release theophylline can be used as a

Table 3 *(continued)*
Dosing Titration (as Anhydrous Theophylline)[a,b,c]

temporary measure. A single 5 mg/kg dose of theophylline in a patient who has not received theophylline in the previous 24 h will produce an average peak serum theophylline concentration of 10 μg/mL (range 5–15 μg/mL). If dosing with theophylline is to be continued beyond the loading dose, the above guidelines should be utilized and serum theophylline concentration monitored at 24-h intervals to adjust final dosage.

Final dosage adjustment guided by serum theophylline concentration

Peak serum concentration	*Dosage adjustment*
<9.9 μg/mL	If symptoms are not controlled and current dosage is tolerated, increase dose about 25%. Recheck serum concentration after 3 d for further dosage adjustment
10–14.9 μg/mL	If symptoms are controlled and current dosage is tolerated, maintain dose and recheck serum concentration at 6–12 mo intervals.[d] If symptoms are not controlled and current dosage is tolerated, consider adding additional medication(s) to treatment regimen
15–19.9 μg/mL	Consider 10% decrease in dose to provide greater margin of safety even if current dosage is tolerated.[d]
20–24.9 μg/mL	Decrease dose by 25% even if no adverse effects are present. Recheck serum concentration after 3 d to guide further dosage adjustment
25–30 μg/mL	Skip next dose and decrease subsequent doses at least 25% even if no adverse effects are present. Recheck serum concentration after 3 d to guide further dosage adjustment. If symptomatic, consider whether overdose treatment is indicated (*see* recommendations for chronic overdosage)
>30 μg/mL	Treat overdose as indicated (*see* recommendations for chronic overdosage). If theophylline is subsequently resumed, decrease dose by at least 50% and recheck serum concentration after 3 d to guide further dosage adjustment

[a]Patients with more rapid metabolism, clinically identified by higher than average dose requirements, should receive a smaller dose more frequently to prevent breakthrough symptoms resulting from low trough concentrations before the next dose. A reliably absorbed slow-release formulation will decrease fluctuations and permit longer dosing intervals.

[b]For products containing theophylline salts, the appropriate dose of the theophylline salt should be substituted for the anhydrous theophylline dose. To calculate the equivalent dose for theophylline salts, divide the anhydrous theophylline dose by 0.8 for aminophylline, by 0.65 for oxtriphylline, and by 0.5 for the calcium salicylate and sodium glycinate salts.

[c]Dosing recommendation taken from Hendeles L, Weinberger M, Szefler S, et al. Safety and efficacy of theophylline in children with asthma. *J Pediatr* 1992; 120: 177–183.

[d]Dose reduction and/or serum theophylline concentration measurement is indicated whenever adverse effects are present, physiologic abnormalities that can reduce theophylline clearance occur (e.g., sustained fever), or a drug that interacts with theophylline is added or discontinued.

and whose bioavailability is insignificantly affected by concomitant food administration are preferred. Once-a-day dosing is inappropriate in most children, who, because of their relatively rapid theophylline clearance, show unacceptable peak-and-trough differences in theophylline concentration and may become symptomatic toward the end of the 24-h dosing interval. With pellet formulations, the beads should be added to moist food (e.g., applesauce) to ensure their dissolution. Sustained-release tablets should not be crushed because this destroys their slow-release properties. An algorithm for initial dosing and final dosage adjustment based on serum concentration measurement may be found in a recent review of safety and efficacy of theophylline in children with asthma (Hendeles et al). Because adverse effects of theophylline become manifest as the serum concentration of 20 μg/mL is approached, it is best to aim for the 8–15 μg/mL range in the majority of patients. It is important to treat the patient and not the theophylline level. Detailed dosing recommendations may be seen in Table 3.

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19 Nonsteroidal Anti-Inflammatory Drugs for the Treatment of Asthma and Allergic Disease

Phil Lieberman, MD

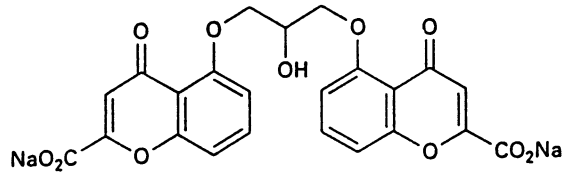
CONTENTS

INTRODUCTION

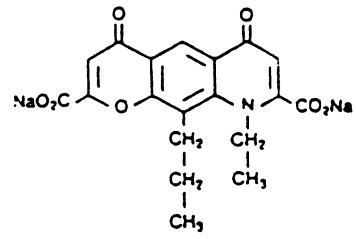
Two drugs, cromolyn sodium and nedocromil sodium, are highly effective agents in the therapy of asthma, allergic rhinitis, and allergic eye disease. They exert their beneficial effects through anti-inflammatory mechanisms and thus have been called nonsteroidal anti-inflammatory agents. They are not, however, chemically or by mechanism related to the prostaglandin synthetase inhibitors commonly referred to as nonsteroidal anti-inflammatory drugs.

These two drugs are not chemically related. Cromolyn sodium is a *bis* chromone, whereas nedocromil is the disodium salt of a pyranoquinoline dicarboxylic acid. Their structures are seen in Fig. 1. Even though these drugs are not structurally related, they both exert remarkably similar anti-inflammatory actions that make them highly useful for therapy of the diseases noted above.

From: *Allergic Diseases: Diagnosis and Treatment*
Edited by P. Lieberman and J. Anderson Humana Press Inc., Totowa, NJ



Sodium Cromoglycate



Nedocromil sodium

Fig. 1. Structural formulae of nedocromil sodium and sodium cromoglycate.

MECHANISMS OF ACTION

A common thread through which these drugs act is thought to be via their effects on the chloride channels of cells. By inhibiting these channels they prevent the activation of a variety of cells involved in the inflammatory process. In nonexcitable cells, the rapid release of intracellular calcium opens chloride channels on the cell's surface. This action induces an influx of chloride ions resulting in, for example, degranulation and mediator release from mast cells or depolarization of sensory neurons.

By blocking the activity of chloride channel pathways on cells, such as mast cells, eosinophils, epithelial cells, endothelial cells, fibroblasts, and sensory neurons, these drugs dampen the inflammatory responses associated with allergic disease. In addition, since similar responses are found in nonallergic asthma, they appear to be effective in this condition as well. Neither agent has intrinsic bronchodilator, anticholinergic, or antihistaminic activity.

In summary, the clinical activity of these drugs appears to be caused by their ability to inhibit the activation of a variety of cells involved in the inflammatory response. The result of this is to interrupt mast cell and neurally mediated symptoms and suppress the activity of the inflammatory cell influx characteristic of allergic disease. Of particular importance is their ability to downregulate the eosinophil-driven inflammatory response. In addition, since these same responses are operative in intrinsic or nonallergic asthma, they can exert a beneficial effect in this condition as well.

USE OF CROMOLYN AND NEDOCROMIL IN ASTHMA

Both of these drugs effectively block the asthmatic response to a variety of stimuli (Table 1). These include not only allergen-induced reactions but also those related to

- Blocks chloride channels thus decreases:
  - Mast cell degranulation
  - Activation of eosinophils
  - Activation of eosinophils
  - Nerve conduction through sensory neurons
- No intrinsic bronchodilator, anticholinergic or antihistamine activity

Key Features of Use in Asthma

- Anti-inflammatory
- Decreases bronchial hyperresponsiveness
- Blocks early- and late-phase reaction
- Prevents reactions to allergic and nonallergic asthmogenic stimuli
- Used as maintenance "preventors"
- Major role is in mild to moderate asthma
- May be corticosteroid sparing
- Superb safety profile
- Superb safety profile

neurogenic, chemical, and physical stimuli, including asthma caused by the inhalation of such substances as substance P, bradykinin, sulfur dioxide, metabisulfite, and fog. In addition, they can prevent exercise-induced bronchospasm. It is thus clear that these agents are more than simple "anti-allergic drugs" since they exert their beneficial effect against a broad variety of asthmogenic challenges.

It is also clear that their action is anti-inflammatory in nature. Biopsy and bronchoalveolar lavage studies both after challenges and during long-term therapy demonstrate very significant reduction in indices of inflammation. Both drugs decrease the amount of eosinophils and activated eosinophils found in bronchoalveolar lavage fluid and on biopsy of the mucosa of the lung. In addition, the amount of albumin in bronchoalveolar lavage fluid is also diminished by treatment with cromolyn sodium.

These *in vivo* effects have been complemented by a number of studies demonstrating clear-cut *ex vivo* effects as well. These include inhibition of release of neutrophil chemotactic factor from macrophages, decreased eosinophil chemotaxis, inhibition of degranulation of eosinophils and mast cells, and numerous other activities.

These observations are accompanied by clear-cut clinical improvement in patients treated with both drugs. This improvement is manifested by a decrease in symptom scores, a gradual increase in forced expiratory volume at 1 s, a decrease in the diurnal variation of peak flow, and a decrease in bronchial hyperresponsiveness to histamine and methacholine challenge. In addition, there is a decrease not only in bronchodilator use but also in the dose of topical corticosteroids necessary to control asthma. These effects are seen not only in allergic asthmatics but also in nonallergic (intrinsic) asthmatics.

Table 1
Asthma-Inducing Agents Backed by Cromolyn and Nedocromil

Allergens
Chemicals (mediators)
Substance P
Capsaicin
Adenosine monophosphate
Neurogenic
Fog
SO_2
Metabisulfite
Exercise
Cold, dry air

Cromolyn sodium has been available for use in the United States since the 1970s. Nedocromil sodium is a more recent addition to our therapeutic armamentarium. Since both drugs are very similar in activity there have been questions regarding whether there are differences between the two that result in relative indications for one versus the other. Although there are no dramatic differences between these two drugs, in clinical practice there appear to be some differences that merit mention. These are summarized in Table 2.

Both drugs, given before allergen challenge, will prevent the early- and late-phase allergic response. However, cromolyn is not effective if given after allergen challenge in preventing the late-phase response, whereas nedocromil is. Both drugs exert their effects on nonallergic asthma stimuli as noted above. Nedocromil, however, seems to be slightly more effective in blocking asthma caused by sulfur dioxide, metabilsulfite, and adenosine monophosphate. In addition, nedocromil may be more effective in inhibiting eosinophil chemotaxis. Specifically, nedocromil sodium, but not cromolyn sodium, can inhibit platelet-activating factor and leukotriene B4-induced chemotaxis of eosinophils.

From a clinical standpoint, however, it is unclear whether the observations noted above result in clinically detectable differences between the two agents. There is, however, some evidence for subtle clinical difference between the two drugs. These are:

1. Nedocromil may have a faster onset of action. In one study it exerted its beneficial effects within a few days, whereas cromolyn may take 2–4 wk.
2. In another study, cromolyn exerted a longer duration of activity in the prevention of exercise-induced asthma.
3. The maintenance dosing frequency of nedocromil may be less than that required for cromolyn. A bid dosing regimen has been found to be effective in some patients using nedocromil.
4. There is some indication that nedocromil may be more effective in nonallergic asthmatics than is cromolyn. There is a rationale for this based on its superior effect in blocking asthma caused by nonallergic stimuli.
5. Nedocromil may have a more potent effect in control of the asthmatic cough.
6. Of importance is the fact that a certain percentage of the population has difficulty taking nedocromil because they taste it. Most patients do not. This taste is not found with cromolyn sodium.

Table 2
Features Distinguishing Nedocromil from Cromolyn

Nedocromil blocks the late-phase pulmonary response to allergy challenge when given either before or shortly after challenge. Cromolyn only does so if given before challenge.
Nedocromil may be more effective in preventing asthma to nonallergic incitants, such as SO_2, metabisulfite, and adenosine monophosphate.
Nedocromil may be more effective in blocking eosinophil chemotaxis.
Nedocromil has a faster onset of action.
Cromolyn may have a longer duration of effect in preventing exercise bronchospasm.
Nedocromil may require a less frequent maintenance dosing regimen.

Despite these observations there is no consistent difference between the two drugs in clinical trials. In some trials they are found equal, in other cromolyn seems to have an advantage in control of certain parameters of asthma, and finally, in other comparisons nedocromil has been slightly superior. Based on an overall analysis of these two drugs for therapy of asthma they seem to be very similar in their activity.

It is important to note that neither drug is a bronchodilator. In addition, both drugs seem to have irritative properties that will cause cough or wheeze in some asthmatic patients when the asthma has not been completely controlled. Thus, as a practical point, before starting these drugs it is best to clear the asthma with a brief course of corticosteroids if the disease is active.

Both drugs are indicated for mild to moderate asthma and, in addition, they appear to have a role in severe asthma to reduce the dependency on topical corticosteroids. Both are indicated for chronic maintenance therapy of asthma. Nedocromil is available in the United States only as a metered-dose inhaler. Cromolyn sodium is available both in a metered-dose inhaler and in a nebulizer solution. Therefore, cromolyn can be used in small children who cannot use a metered dose inhaler.

Initially, both drugs should be given when the asthma is under control and utilizing a qid regimen. A reduction in dosage frequency is almost always possible for maintenance therapy. A unique use for both drugs is prior to allergen exposure, such as before visiting a relative with a pet to whom the patient is allergic. Both should be given before exposure and every 4 h while exposed. Both drugs are effective agents to prevent exercise-induced bronchospasm. They are given immediately before exercise.

ALLERGIC RHINITIS

Both nedocromil and cromolyn sodium are effective agents in the therapy of allergic rhinitis in both its seasonal and perennial forms. However, nedocromil is not available in the United States for treatment of rhinitis and therefore this discussion will be limited to the use of cromolyn sodium. Cromolyn sodium is available in an aqueous form for the therapy of allergic rhinitis. As with asthma, the administration of cromolyn sodium results in prevention of both the early and late nasal response to allergen inhalation and a decrease of activated and total eosinophils in nasal secretions and biopsies.

As in the therapy of asthma, the drug should be given when the rhinitis is under reasonably good control. It should be given prior to exposure. Thus, if used to treat sea-

Useful in Therapy of Allergic Rhinitis in Perennial and Seasonal Forms and in Treatment of Allergic Eye Disorders

- Seasonal allergic conjunctivitis
- Vernal keratoconjunctivitis
- Atopic keratoconjunctivitis
- Giant papillary conjunctivitis

sonal allergic rhinitis, the therapy should be initiated before the allergy season begins. The drug can be highly effective in blocking symptoms resulting from isolated allergy exposure. Therefore, it can be given immediately before mowing the lawn or visiting a relative with a pet.

It is important to note that the drug does not exert an immediate effect but is a preventive agent and needs to be used regularly during allergen exposure. It is initiated in a qid dosage regimen. This dosage frequency can be reduced in most patients after the first 2–3 wk of therapy. As with asthma, its safety profile is superb. Therefore, it is an excellent drug for use in children where there is a desire to avoid topical corticosteroids.

ALLERGIC EYE DISEASE

Cromolyn sodium has been found effective in the management of several allergic eye diseases. All of these are characterized by a putative role for mast cells and eosinophils. These conditions include seasonal allergic conjunctivitis, vernal keratoconjunctivitis, atopic keratoconjunctivitis, and giant papillary conjunctivitis (contact lens conjunctivitis).

SEASONAL ALLERGIC CONJUNCTIVITIS

Cromolyn has been shown to be approximately as effective as antihistamines in the therapy of seasonal allergic conjunctivitis. It reduces symptoms of itching, stinging, grittiness, and sensitivity to light. Response in seasonal allergic conjunctivitis may be related to IgE antibody levels to specific aeroallergens. In one study a significant correlation between pretreatment specific antiragweed IgE and the response to cromolyn sodium was noted.

As with other allergic diseases, the drug should be started before exposure when the patient is relatively free of symptoms. It is administered at a dose of 1–2 drops qid. Cromolyn sodium can also be used, as with asthma and rhinitis, before specific allergen exposure.

VERNAL KERATOCONJUNCTIVITIS

Vernal keratoconjunctivitis is a recurrent, bilateral, interstitial inflammation of the conjunctiva. It is more frequent in warm, dry climates. Most of the patients are under 15 yr of age.

Several studies have evaluated the use of cromolyn sodium in vernal keratoconjunctivitis and have found the drug to be effective. The beneficial effect seems to occur

within a week after the initiation of therapy and can be detected by a decrease in pruritus and mucus secretion. As with seasonal allergic rhinitis, the dose is 1–2 drops qid.

ATOPIC KERATOCONJUNCTIVITIS

Atopic keratoconjunctivitis is a condition associated with atopic dermatitis. The symptoms include itching, burning, mucoid discharge, and light sensitivity. Double-blind placebo-controlled crossover studies of cromolyn sodium have shown a beneficial effect in discharge, photophobia, papillary hypertrophy, limbal changes, and corneal changes. In addition, a reduction in topical corticosteroid use has been noted.

GIANT PAPILLARY CONJUNCTIVITIS (CONTACT LENS CONJUNCTIVITIS)

Although the cause of giant papillary conjunctivitis has not been established, there is evidence suggesting that the process is triggered by an inflammatory response to any foreign substance in the eye. Pathologic changes in many patients are similar to those seen in documented allergic eye disorders. Because of this observation, cromolyn sodium has been tried as a therapeutic agent. A reduction in symptoms and an increased tolerance to contact lens wear has been demonstrated in many patients. The dose is the same as for other ocular disorders.

SAFETY AND SIDE EFFECT PROFILES

Nedocromil and cromolyn sodium are two of the safest drugs available for treatment of allergic diseases. They exert very little, if any, acute, subacute, or chronic toxicity. Although there have been reports of local irritation and cough with asthma, nasal irritation with nasal administration, and burning on instillation with the ophthalmic solution, no consistent severe side effects have been noted. Nedocromil, as discussed above, is tasted by certain patients. This, in many instances, limits its use.

SUMMARY

Both nedocromil and cromolyn sodium are useful anti-inflammatory drugs in the therapy of allergic diseases. These diseases include asthma, allergic rhinitis, and allergic ocular disorders. In the United States, nedocromil and cromolyn sodium are both available for the therapy of asthma, but only cromolyn sodium is available for treatment of the other conditions.

Both drugs are indicated in the use of mild to moderate asthma and in patients who are steroid-dependent asthmatics. They are effective in reducing symptoms, improving lung function, and decreasing bronchial hyperreactivity. In addition, they both can be used prior to isolated allergen exposures. They have particularly useful roles in children where there is a strong wish to avoid topical corticosteroids. Their efficacy in mild to moderate asthma appears to be equivalent to that of low dose topical corticosteroids. Both drugs should be administered initially when the illness treated is under relatively good control and both need to be used on a regular basis as "maintenance therapy". Neither drug has intrinsic bronchodilator, antihistamine, or anticholinergic activities. Therefore, neither drug is useful in the treatment of acute symptoms. This is true not

only for asthma but for rhinitis and ocular disorders as well. Both have an excellent safety profile and no consistent significant adverse reactions occur with either drug.

ACKNOWLEDGMENT

Dr. Peter Creticos is acknowledged for his assistance in the formulation of an earlier version of this chapter.

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20 Anticholinergic Agents

Phil Lieberman

CONTENTS

HISTORY

Anticholinergic agents, derived from plant alkaloids, have been used for medicinal purposes for hundreds of years. They were introduced to Western medicine by the British in the 1800s, and gained wide popularity as inhaled agents (smoked through pipes or cigarets) for the therapy of asthma and bronchitis during the 1800s and early 1900s. As adrenergic agents were developed their use declined. However, over the past three decades, there has been a renaissance in the use of anticholinergic agents for respiratory disorders. There are two reasons for their reintroduction into our therapeutic armamentarium. These are our advances in knowledge regarding the role of the parasympathetic nervous system in respiratory disease and the development of anticholinergic agents that have increased effectiveness with decreased side effects. This has been accomplished by alterations in the structure of the naturally occurring belladonna alkaloid, atropine. The major structural change, favorably altering the efficacy and side effect profile of atropine, is the introduction of a quaternary ammonium congener, ipratropium bromide (Fig. 1). The quaternary ammonium structure of ipratropium bromide differs from that of atropine in that the nitrogen atom is pentavalent and has a positive charge.

From: *Allergic Diseases: Diagnosis and Treatment*
Edited by P. Lieberman and J. Anderson Humana Press Inc., Totowa, NJ

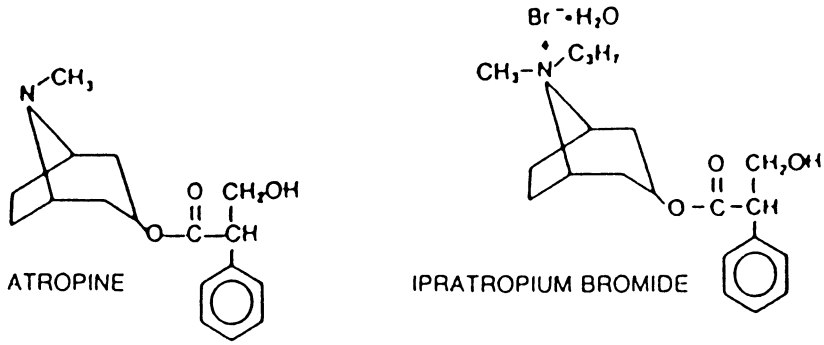

Fig. 1. Structures of atropine and ipratropium bromide.

PHYSIOLOGY AND PHARMACOLOGY OF THE PARASYMPATHETIC NERVOUS SYSTEM

The respiratory tract is innervated by cholinergic nerve fibers that proceed through the vagus nerve into both the upper and lower airways. Fibers supplying the nose travel through the vidian nerve and innervate mucous and serous glands as well as arteries and veins. Fibers traversing the vagus synapse in ganglia located in the airway walls. From there, short postsynaptic fibers supply glands and airway smooth muscle.

Stimulation of the vagus results in the release of acetylcholine from these nerve terminals. This in turn activates receptors in the airways that produce well known cholinergic effects. In the lungs these are bronchoconstriction and mucous secretion. In the nose they are hypersecretion and, to some extent, vasodilatation.

It has long been known that atropine prevents the effect of vagal stimulation on smooth-muscle and exocrine glands. On the other hand, atropine has very little effect on the actions of acetylchooline on ganglia or skeletal muscle. Since the alkaloid muscarine mimics the effect of acetylcholine on glands and smooth muscles, atropine is actually an antimuscarinic rather than an anticholinergic drug *per se*. That is, it only blocks the muscarinic activity of acetylcholine and not those mimicked by nicotine (nicotinic activity) occurring at ganglia and skeletal muscle.

It is now known that there are several muscarinic receptor subtypes (M1–M5). Airway receptor subtypes are of the M1, M2, and M3 varieties. The lung contains all three of these, whereas the nose contains only M1 and M3 receptors.

The precise function of these receptors is yet to be defined but it is probable that M1 receptors enhance cholinergic transmission, M2 receptors, which are located in ganglion, exert a negative feedback control, and M3 receptors cause smooth-muscle contraction in the lung, glandular secretion in both upper and lower airways, and probably dilate blood vessels (producing nasal constriction) in the nose (Table 1). Thus, it can be seen, based on the physiologic consequences of cholinergic stimulation, that there is great rationale for the use of anticholinergic agents in the therapy of both nasal and pulmonary disease.

Table 1
Location and Function of Muscarinic Receptors in the Airways

Receptor	*Location*	*Function*
M1	Alveoli, glands, ganglia	Enhances transmission
M2	Postganglionic nerves	Negative feedback Reduces transmission
M3	Smooth-muscle lung	Contraction smooth-muscle
	Glands	Secretion mucous and serous glands
	Blood vessels nose	Vasodilatation?

ANTICHOLINERGIC AGENTS

For many years clinicians employed atropine and glycopyrrolate for therapy of asthma and rhinitis. Atropine was diluted in saline and used as a nasal spray for rhinitis and as an aerosol in the treatment of status asthma. Glycopyrrolate was also used in the treatment of status asthma. However, the use of these drugs was limited by the fact that they were absorbed from the respiratory tract and therefore could exert systemic effects. The use of quaternary ammonium congeners alter the side effect profile and increase the efficacy of atropine and glycopyrrolate. Worldwide there are three such drugs available. These are atropine methylnitrate, oxitropium bromide, and ipratropium bromide. Oxitropium bromide is a congener of scopolamine, whereas ipratropium bromide is a congener of atropine. In the United States, however, only Ipratropium bromide (IB) is available. Thus, the following discussion will be limited to this drug.

IB has several distinct advantages over atropine. These are noted in Table 2. Atropine is a naturally occurring alkaloid that is an organic ester of tropine and tropic acid. It is widely distributed in nature, found especially in the Solanaceae plants. The structure of IB is based on that of atropine. The structural change consists of the addition of a bromide ion and the conversion of the nitrogen atom to a pentavalent state associated with a positive charge. This conversion results in several therapeutic advantages. IB is insoluble in lipids (although freely soluble in water, like atropine sulfate) and therefore crosses biological barriers with difficulty (unlike atropine, which crosses such barriers easily). Therefore, IB is not absorbed to any extent from the respiratory or gastrointestinal tract, as is atropine. In addition, whereas atropine crosses the blood-bearing barrier, IB does not. These features markedly reduce the side effect profile of IB compared to atropine. They therefore allow for larger doses to be given without adverse effect. The effectiveness of this drug is enhanced since it is innately approximately twice as potent a bronchodilator as atropine. Also, IB does not, in contrast to atropine, decrease mucociliary clearance. On the other hand, neither drug is selective for a particular type of muscarinic receptor. The sum total of the differences between IB and atropine results in an increased efficacy with complete elimination or a marked decrease in side effects, such as dry mouth, central nervous system changes, tachycardia, and mydriasis.

Three different IB preparations are available for use. These are all marketed under the trade name of Atrovent. The preparations are an aqueous nasal spray for rhinitis, an

- Anticholinergic (antimuscarinic) drugs exert their effect at the target organ to block secretion and smooth-muscle contraction in the respiratory tract
- Ipratropium bromide is the only anticholinergic agent available in the United States at this time
- Approved indications for ipratropium bromide are:
  - Upper respiratory infection
  - Perennial rhinitis
  - Maintenance therapy of chronic bronchitis and emphysema
- It can also be useful in:
  - As a maintenance bronchodilator in select cases of asthma
  - In management of exacerbations of asthma and chronic obstructive pulmonary disease in combination with a β-adrenergic
  - Gustatory rhinitis

Table 2
Comparison of Ipratropium Bromide (IB) and Atropine (A)

	IB	*Atropine*
Synthesis	Synthetic analog of atropine	Naturally occurring
Structure	Quaternary ammonium congener of atropine	Organic ester combination of tropic acid and tropine
Water soluble	Yes	Yes
Lipid soluble	No	Yes
Absorbed from gastrointestinal tract	No	Yes
Absorbed from respiratory tract	No	Yes
Enter central nervous system	No	Yes
Decrease mucociliary clearance	No	Yes
Selective for muscarinic subtype receptors	No	No

aqueous solution for obstructive lung disease, and a metered dose inhaler, also for obstructive lung disease. All of these drugs share the same mechanism of action, the inhibition of parasympathetic stimulation at target organ receptor sites. This appears to be accomplished by preventing increases in intracellular concentrations of cyclic guanosine monophosphate (cyclic GMP) produced by muscarinic receptor stimulation.

USE OF ANTICHOLINERGIC DRUGS IN THE THERAPY OF RHINITIS

Atrovent nasal spray has official indications for use in the treatment of perennial rhinitis of allergic and nonallergic origin as well as the common cold. In addition, it is commonly used to treat patients with gustatory rhinitis or "skiers/joggers nose" and is

often used in seasonal allergic rhinitis as well. It is officially indicated for only one symptom, rhinorrhea. However, clinical studies have shown that patients attain beneficial effects regarding nasal congestion and sneezing as well. The stated effect on nasal congestion is consistent with the observations that M3 receptors appear to be present on nasal blood vessels and that cholinergic stimulation can result in some degree of nasal dilatation.

The drug is available in 0.03% and 0.06% concentrations. The 0.03% dose is indicated for chronic rhinitis and the 0.06% for the common cold. The nasal spray delivers 21 μg of the 0.03% concentration and 42 μg of the 0.06% concentration per actuation. It is dispensed as a fine aerosol via a manual pump. The volume of each spray is 70 μL. This is calculated to sufficiently fill the nasal passage without "runoff" anteriorly or the production of posterior nasal drainage. The recommended dose of the 0.06% preparation is two sprays (84 μg) per nostril tid to qid for a total dose of 504–672 μg/d. The dose of the 0.03% preparation is two sprays (42 μg) per nostril two to three times daily for a total dose of 168–252 μg/d. Neither concentration, at this time, has received official approval for use in patients under 12 yr of age.

In the treatment of chronic rhinitis, the effect of IB has been found to be additive to that of topical nasal steroids (beclomethasone) and antihistamines (terfenadine). It appears to be effective in both nonallergic and allergic rhinitis. It has a relatively rapid onset of action (usually within the first 24 h), and it is relatively free of side effects. As expected, patients with profuse rhinorrhea seemed to get the most benefit from this drug.

A particularly unique use for anticholinergic agents is in the treatment of forms of rhinorrhea mediated purely through vagal stimulation. These are commonly referred to as gustatory rhinitis or skiers/joggers nose. In this instance the patient suffers from profuse nasal discharge precipitated by eating or by exposure to cold air. Similar forms of rhinitis can occur on exposure to respiratory irritants, such as sulfa dioxide. IB is particularly effective in such cases if administered approx 1 h before exposure to the inciting stimulus (0.06%, 2 sprays each nostril). The salient features of IB as used in rhinitis are noted in Table 3.

ANTICHOLINERGICS FOR USE IN OBSTRUCTIVE LUNG DISEASE

Three preparations of IB are available for use in Europe for the therapy of obstructive lung disease. Two preparations are available in the United States at the time of this writing. The third preparation, Combivent, which is Atrovent in combination with albuterol, is scheduled to be released in the United States shortly. Officially, both preparation available in the United States are for use in the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. Neither drug has been approved for use in asthma. However, both preparations have been used for therapy in asthma and in selected cases may be of benefit.

The metered dose inhaler comes in a 14-g vial providing 200 inhalations. Each actuation delivers 18 μg of IB from the mouthpiece. The usual starting dose is two inhalations (36 μg) qid. Patients, however, often require additional inhalations. The maximum recommended amount is no more than 12 puff/24 h. The inhalation solution is available

Table 3
Ipratropium Bromide in Rhinitis

Indication	Perennial rhinitis and the common cold are approved indications; also used in gustatory rhinitis and skiers/joggers nose—*see text*
Preparations	0.03% for perennial rhinitis 0.06% for the common cold
Dose	0.03% for perennial rhinitis 2 sprays (42 μg) each nostril b.i.d. to t.i.d. 0.06% for the common cold 2 sprays (84 μg) each nostril t.i.d. to q.i.d.
Contraindications	Only hypersensitivity to agent or other ingredient
Precautions	Avoid spraying into eye
Miscellaneous	Added benefit when used in combination with antihistamine or topical corticosteroid Useful in gustatory rhinitis or skiers/joggers nose (0.06%, 2 sprays each nostril 1 h before)—*see text*

in unit dose vials with one single dose (500 μg) per unit. The dose is one unit tid to qid by nebulization. The metered dose vial contains 500 μg of IB in 2.5 mL of normal saline.

As noted, both preparations are indicated officially only for emphysema and bronchitis. They appear to be the bronchodilator of choice in both of these conditions. Neither, however, is officially indicated for treatment of acute episodes of these diseases. Nonetheless, the inhaled solution is commonly used for acute exacerbations.

It is quite clear that although IB is less effective than β-2 agonists in producing bronchodilatation in asthma, the drug does exert a bronchodilator effect that can be additive, in some patients, to β-adrenergic inhalation. Therefore, in select patients, usually those not adequately responding to therapy with an inhaled β-agonist and topical corticosteroids, IB may be an effective agent. In addition, it may be useful in asthma as a maintenance bronchodilator for those patients who cannot discontinue β-adrenergic blocking agents and for select patients in whom there is a strong psychogenic or vagally mediated reflex component to their bronchospasm.

The inhaler solution is very useful for therapy of acute exacerbations of asthma. It is not to be used as a single bronchodilator, but rather in combination with a β-agonist. A convenient dosage regimen is to add the β-agonist directly to the IB in the nebulizer. The combination of IB and a β-adrenergic agent administered by compressor nebulizer is more effective than either agent alone. It should, however, be clear that IB alone is not as effective as a β-adrenergic agent in the therapy of asthma, but is superior for maintenance bronchodilation in the therapy of chronic obstructive lung disease.

The onset of bronchodilation after inhalation of IB is delayed (15 min) as compared with β-agonists. However, it may be more prolonged than the short-acting β-2 agonists. The duration of effect of IB can be 6–8 h. Its usefulness as a drug for asthma is accentuated by the fact that it is available in combination therapy with albuterol in Europe. Salient features of ipratropium bromide as a bronchodilator are seen in Table 4.

Table 4
Ipratropium Bromide in Chronic Obstructive Lung Disease

Indication	Approved in United States only for emphysema and bronchitis. However can be beneficial in combination with a β-agonist for maintenance therapy in some asthmatics and for acute exacerbations of asthma
Preparations	Metered dose inhaler and inhaler solution[a]
Dose	Metered dose inhaler—starting dose 2 puffs (36 μ)g qid Solution—500 μg (2.5 cc) tid to qid
Miscellaneous	• If used in asthma should be combined with a β-agonist. May add the β-agonist directly to the nebulizer solution if used within 1 h • May be of benefit in asthma as a primary bronchodilator in patients who are on β-blocker • Onset of action slower than β-agonist. Therefore may not be suitable as "rescue medication"

[a]Combivent, IB in combination with Albuterol, is scheduled to be released in the United States.

SIDE EFFECT PROFILE OF IPRATROPIUM BROMIDE

As a whole, this drug is remarkably free of side effects. Because of its failure to cross biological barriers it exerts no significant systemic side effects in inhaled forms. Side effects are for the most part, therefore, limited to local manifestations. Administered as a drug for bronchodilatation, its most common side effects are cough with bronchial irritation. Headache has been reported as well. Adverse reactions by nasal spray include epistasix, dry mouth, and throat and nasal dryness. Care should be taken when using any preparation not to spray the drug directly into the eye. It can cause mydriasis and pain.

Although lipid insoluble quaternary bases can enter breast milk, the amount of ipratropium systemically absorbed makes it unlikely that any significant amount will be found in breast milk. However, it is recommended that, because these drugs can be excreted in human milk, caution should be exercised. All preparations of ipratropium bromide are listed under pregnancy category B.

SUMMARY AND CONCLUSION

Ipratropium inhalation therapy is useful both by nasal and pulmonary routes. Intranasal administration is especially useful for patients with profuse rhinorrhea. However, in studies assessing symptom improvement, many patients claim to have amelioration of other symptoms, including congestion, sneezing, and postnasal drainage. The drug is officially approved for use in perennial rhinitis as well as the common cold. It is also useful in gustatory rhinitis.

IB is the bronchodilator of choice for maintenance bronchodilatation in emphysema and bronchitis. It does not have an official indication for therapy of asthma but may be helpful in some patients for chronic maintenance. In addition, it is useful in the therapy of acute exacerbations administered via compressor nebulizer in combination with a β-adrenergic agent. Because of the poor systemic absorption it has an excellent side effect profile.

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21 Glucocorticoid Therapy in Asthma

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CONTENTS

INTRODUCTION

GC therapy is a valuable treatment modality in the management of both acute and chronic of asthma. GCs were first used in the treatment of asthma shortly after cortisone was first synthesized and following reports that cortisone was effective in the treatment of rheumatoid arthritis. Early studies evaluating the effect of cortisone on asthma were encouraging, with significant improvements in asthma symptoms and pulmonary function. Much of the early enthusiasm for systemic GC use was dampened with the realization that chronic use of this medication resulted in multiple adverse effects. The subsequent development of effective inhaled GC preparations has revolutionized asthma care. By virtue of their high topical to systemic potency, inhaled GC therapy has proven to be safe and effective in the treatment of asthma. This chapter will provide a broad overview of the structure, mechanisms of action, pharmacokinetics, efficacy, and adverse effects associated with systemic and inhaled GC therapy in asthma.

From: *Allergic Diseases: Diagnosis and Treatment*
Edited by P. Lieberman and J. Anderson Humana Press Inc., Totowa, NJ

- Glucocorticoids (GCs) are the most effective therapy for allergic disease.
- In asthma, topical GCs decrease bronchial hyperresponsiveness when given long term.
- In therapy of acute exacerbations of asthma, the early institution of systemic GC therapy can prevent emergency room visits and hospitalization.
- In patients with chronic severe asthma who require regular systemic GC therapy, all other treatments should be maximized and the lowest dose sufficient for control should be established through regular monitoring visits.

CHEMISTRY

Synthetic glucocorticoids are cortisone-based molecules that have undergone structural modifications designed to enhance their potencies and prolong their durations of action. Anti-inflammatory glucocorticoids have a 17-hydroxyl group and methyl groups at carbons 18 and 19 (Fig. 1). Other features necessary for activity are a ketone at carbons 3 and 20, a double bond between carbons 4 and 5 of the A-ring, and a hydroxyl group at the 11-position of the C-ring. Modifications to the basic steroid structure have increased the anti-inflammatory while decreasing mineralocorticoid effects; however, it has not been possible to separate the unwanted metabolic effects while retaining the desired anti-inflammatory properties of the synthetic glucocorticoids that are systemically administered. Further modification of inhaled GC preparations by fluorination of the 6 or 9 carbons of the B-ring have resulted in greater anti-inflammatory effects of these compounds (Fig. 1).

MECHANISMS OF ACTION

As discussed in previous chapters, asthma is a chronic respiratory disease characterized by reversible airflow limitation and airway hyperresponsiveness to a variety of stimuli in which airway inflammation is thought to play a significant role. Given that inflammation plays an important role in the pathogenesis of asthma, drugs that interfere with the inflammatory response should be effective in the treatment of this disease. Thus, it is not surprising that by virtue of their anti-inflammatory properties GCs have become the cornerstone of asthma therapy.

Although a great deal of research over the past 20 years has improved our understanding, the precise mechanism(s) by which GCs suppress inflammation is not clear. Recent studies have indicated that GCs act at several levels in the inflammatory response (Table 1). The anti-inflammatory properties of GCs come mainly from their ability to inhibit the expression and/or production of molecules involved in the initiation and maintenance of the inflammatory response. Specifically, they inhibit the upregulation of adhesion molecules on endothelial cells, which are required for the adhesion and subsequent migration of inflammatory cells to sites of inflammation. They also inhibit the production of cytokines, such as IL-1, IL-2, IL-4, IL-5, IL-6, tumor necrosis factor alpha (TNFα), and interferons involved in inflammatory cell recruitment, activation, and proliferation. The release of potent lipid mediators of inflammation, such as platelet

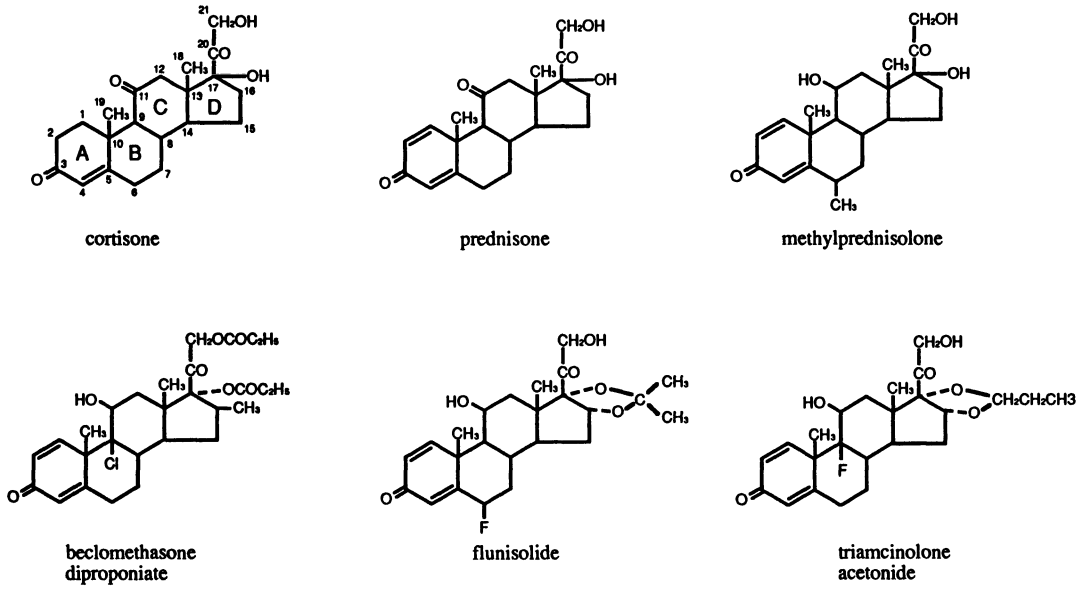

Fig. 1. Molecular structures of glucocorticoids commonly used in the treatment of asthma. Carbon and ring nomenclature are noted for cortisone.

Table 1
Mechanisms of GC Action in Asthma

Inhibitory effects
Inhibition of leukocyte adhesion/migration
Inhibition of leukocyte activation, function, and survival
T-lymphocytes
Eosinophils
Monocyte/macrophages
Inhibition of the production of cytokines important in the differentiation, proliferation, and activation of inflammatory cells
IL-2, IL-3, IL-4, IL-5
Inhibition of the production and/or release of inflammatory mediators
1. Lipid mediators (platelet activating factor, leukotrienes, prostaglandins)
2. Cytokines (IL-1, IL-6, TNFα)
3. Eosinophil-derived cytotoxic proteins (major basic protein, and so forth)
Positive Effects
Stimulation of lipocortin expression— inhibition of arachadonic acid metabolite synthesis
Vasoconstrictive properties
Decreased edema
Less extravisation of proinflammatory mediators
Potentiation of β-adrenergic receptor
Heightened response to β-agonists

activating factor, leukotrienes, and prostaglandins, are also inhibited by GCs. GCs also display potent vasoconstrictive properties. By decreasing capillary permeability at sites of inflammation, less plasma exudation occurs, resulting in a reduction in the concentration of inflammatory and chemotactic factors and ultimately in a decrease in the inflammatory response. Another salutory effect of GC therapy that is especially relevant to asthma is the potentiation or upregulation of airway β-adrenergic receptors.

PHARMACOKINETICS

The pharmacokinetics of glucocorticoids, including absorption, distribution, and elimination, are important determinants of the magnitude and duration of action. These factors can influence dosing strategies; however, in general, glucocorticoid dosing regimens are not dependent on pharmacokinetic parameters. Dosing is empirical or based on the patient's history of prior responses. Exceptions to this are when gross abnormalities of absorption or elimination, as with some drug interactions, result in a clinically significant reduction of systemic glucocorticoid exposure. In this scenario, clinical response to treatment would be expected to be diminished. Prednisone, prednisolone, and methylprednisolone are all rapidly and nearly completely absorbed following oral administration with peak plasma concentrations for prednisone/prednisolone occurring within 1–2 h, whereas peak levels occur 2–4 h postdose for methylprednisolone. Absorption of GCs is, in general, not affected by age, disease states, or smoking. Concomitant antacid administration and chronic active liver disease are two situations that can reduce the bioavailability of prednisolone. Of note, prednisone is an inactive prodrug and requires biotransformation of the 11-ketone group to an 11-hydroxyl group. This conversion to prednisolone (its active form) occurs via first-pass hepatic metabolism. Once absorbed, GCs bind to various proteins with prednisolone binding primarily to transcortin, albumin, and α1-acid glycoprotein, whereas methylprednisolone binds primarily to albumin. As a result, greater penetration and longer retention in lung tissue have been reported with methylprednisolone, and may represent a therapeutic advantage in the treatment of asthma and other pulmonary diseases.

Following absorption, GCs are metabolized into inactive compounds in the liver. The rate of metabolism or clearance of a GC can be altered by drug interactions and disease states. Hyperthyroid patients require higher glucocorticoid doses owing to enhanced nonrenal clearance and reduced metabolism. With hypothyroid patients, slowed elimination is a concern; however, this has not been well studied. Asthma is not thought to affect metabolism of GCs, although conflicting data have been reported. Glucocorticoid elimination may also be altered by numerous concomitant medications (Table 2). Drug interactions may result in either reduced or enhanced clearance, and consequently an increased risk for adverse effects or a diminished therapeutic response, respectively. The anticonvulsants, phenytoin, phenobarbital, and carbamazepine, cause an increased rate of elimination for dexamethasone, prednisolone, and methylprednisolone. Of note, methylprednisolone clearance is most significantly affected. Rifampin, like the above anticonvulsants, enhances the clearance of GCs and can result in a diminished therapeutic effect and breakthrough asthma symptoms in the steroid-dependent patient.

In contrast to anticonvulsants and rifampin, other medications can reduce GC elimination. Significant reductions in clearance have been noted with concomitant ketocona-

Table 2
Clinically Significant Drug Interactions with Systemic GCs

GC	*Drugs that increase clearance*	*Drugs that decrease clearance*
Methylprednisolone	Carbamazepine	Ketoconazole
	Phenobarbital	Troleandomycin
	Phenytoin	
	Rifampin	
Prednisolone	Antacids (decrease absorption)	Ketoconazole
	Carbamazepine	Oral contraceptives
	Phenobarbital	
	Phenytoin	
	Rifampin	
Dexamethasone	Carbamazepine	
	Phenobarbital	
	Phenytoin	

zole administration. Erythromycin and troleandomycin can also delay glucocorticoid clearance; however, this effect is limited to methylprednisolone. Clearance can be reduced by 70% with concomitant troleandomycin therapy, and although not yet reported, this interaction may occur with the newer macrolide antibiotics as well. In addition, a 50% reduction of prednisolone elimination can be expected with coadministration of oral contraceptives.

If a drug interaction that increases clearance is identified, one can simply increase the dose. This strategy may not always result in therapeutic benefit, however. The most obvious step in optimizing response to GC therapy is to discontinue the interacting medication. Often this may not be feasible, and other interventions are required. One such option would be to change to another GC that is less susceptible to the interaction. In the case of interacting anticonvulsants, this would constitute switching from methylprednisolone to prednisone or prednisolone.

Glucocorticoid pharmacokinetics studies have been performed in asthmatic patients who respond poorly to therapy (with no obvious drug interactions present) to assess their absorption and clearance of GCs and rule out pharmacokinetic abnormalities as contributing factors to their poor response. A small subset of patients have inherently rapid clearance of prednisolone or methylprednisolone. These patients often display few steroid-associated adverse effects and present with a history of poor response to GC therapy. In these patients a simple change in glucocorticoid may elicit an improved response. In others, a "split" dosing regimen consisting of two-thirds of the total daily GC dose in the morning with the remaining one-third administered in the afternoon would provide for a more normal plasma concentration vs time curve and could result in better responsiveness. This strategy might also be beneficial in patients in which an interacting medication (anticonvulsants, rifampin) might be present. If these changes offer no benefit, a change to a GC with a longer half-life, such as dexamethasone, could be another option, keeping in mind that the potential for adverse effects may increase.

PHARMACODYNAMICS

Pharmacodynamics is the study of drug action, and can be measured with regard to onset of action, peak effect, duration of effect, and offset of action. Provided glucocorticoids are not hindered by abnormally influenced pharmacokinetics and reach the target tissues in adequate concentrations, a number of steps at the molecular level are required for them to exert their biological effects. These likely contribute to the slow onset and slow dissipation of effects that characterize GC actions. This principle is consistent with observed responses of patients with asthma following systemic administration of GCs. In asthmatics given a single dose of 40 mg of prednisolone, onset of improved pulmonary function was observed 3 h after administration with a maximal effect at 9–12 h postdose followed by a gradual return to near baseline values at 36 h postdose.

A number of models have been used to examine the effects of different dosing strategies on the pharmacodynamics of GCs, and it has been demonstrated that larger doses merely extend the duration of effect rather than the maximal intensity of response. Smaller doses of GCs given more frequently appear to provide more effectiveness than single large doses. Thus, the frequency of dosing may be more important than actual dose administered. With systemically administered GCs, comparisons of low and high doses for acute severe obstruction have not always shown a clear benefit with high-dose therapy.

EFFICACY OF ORAL GC THERAPY IN ASTHMA

Effect on Bronchial Hyperresponsivenss

Increased bronchial responsiveness, or bronchial hyperresponsiveness (BHR), is a sentinel feature of asthma that has been shown to correlate with disease severity, frequency of symptoms, and need for treatment. Although the precise relationship remains elusive, airway inflammation is thought to contribute to BHR. Oral GCs have been demonstrated to abolish the heightened BHR associated with in vivo allergen exposure and to diminish nonspecific BHR caused by methacholine when given in large doses. Specifically, high-dose prednisone therapy has been shown to improve both pulmonary function and lessen BHR in children with atopic asthma. Similar results have been noted in studies of adult asthmatics. Reductions in BAL fluid eosinophil counts and reductions in the number of inflammatory cells expressing mRNA for cytokines involved in allergic inflammation have also been associated with diminished BHR following high-dose prednisone therapy in adult asthmatics. These observations suggest that GCs, by inhibiting cytokine synthesis, inhibit airway eosinophilia and subsequently lessen BHR. As will be discussed in a subsequent section, multiple studies have also shown inhaled GC therapy to lessen BHR. Thus, GCs, by oral or inhaled route, have beneficial effects on reducing the degree of BHR in patients with asthma. It has been suggested that by decreasing BHR, GC therapy can decrease both the onset and severity of asthma attacks, thereby potentially reducing the morbidity and mortality of asthma.

Effects of Systemic GC on Acute Exacerbations of Asthma

In 1956, soon after the first case reports showing a beneficial effect of GC in asthma were published, the first placebo-controlled study demonstrating the efficacy of sys-

temic GC therapy was published. Since that initial report, multiple studies in both adults and children have been performed; most have demonstrated efficacy, whereas a minority have failed to show significant differences between GC and placebo. Two recent reviews, one by McFadden *(1)* and the other by Engle and Heinig *(2)* nicely summarize the studies evaluating the efficacy of GC therapy in acute asthma.

Acute Asthma in Adults

Studies evaluating the effectiveness of GCs in the emergency room management of acute asthma have shown that a single dose of iv methylprednisolone can decrease the need for subsequent hospitalization. The majority of studies that have evaluated the effectiveness of iv GC therapy in hospitalized patients have shown GC therapy to be superior to placebo as measured by improvement in pulmonary function and symptoms. Despite their widespread use, the optimal dose of GC in the acute setting has not been firmly established. Some studies have demonstrated a dose–response effect with higher doses of GC being more effective than lower doses. Unfortunately, many of the studies have not included a placebo-matched group, which would help determine the extent of spontaneous improvement in lung function independent of GC therapy. Just as there is no clear consensus regarding the appropriate dose of GC in acute asthma, there is no consensus regarding the duration of GC treatment. Since duration of treatment is in part related to the severity of the initial episode, recommendations for the length of treatment must be tailored to the individual case. With that in mind, it has recently been recommended to treat patients admitted in status asthmaticus with at least 36–48 h of iv therapy with a transition to oral GC therapy when tolerated. The duration of the oral GC taper again will depend on the individual's response, but should span 4–12 d. The duration of GC taper following an acute asthma exacerbation often remains emperic, but is again largely dependent on the severity and duration of the exacerbation.

Studies evaluating short courses of prednisone for acute asthma exacerbations in the outpatient setting have shown prednisone to be more effective than placebo at reducing the number of relapses requiring further medical care for increasing asthma symptoms. Those patients with the greatest degree of airflow obstruction at the initial visit are most likely to receive the most benefit from prednisone therapy.

In summary, multiple studies have shown systemic GC to be a highly effective therapy in acute asthma, yet a clear consensus on the optimal type, dose, route of administration (oral vs iv), and duration of treatment does not exist. A number of protocols outlining systemic GC therapy in acute asthma have been published. Keep in mind that therapy should be tailored to the individual patient's condition. The National Heart, Lung, and Blood Institute (NHLBI) has recently published guidelines established by an expert panel of asthma specialists. This document recommends methylprednisolone 60–80 mg iv every 6–8 h, hydrocortisone 2 mg/kg iv every 4–6 h, or hydrocortisone 2 mg/kg iv bolus followed by 0.5 mg/kg/h continuous iv infusion for the treatment of acute severe asthma. Oral methylprednisolone or prednisone is also recommended as a substitute for iv GC with the recommendation made to administer 60 mg initially, followed by 60–120 mg/d in divided doses and tapered over several days at the discretion of the physician. The NHBLI guidelines are not specific with regard to the duration of GC treatment. McFadden *(1)* in a recent analysis of GC therapy in acute asthma, provides a more complete dosing schedule (*see* the review by McFadden *[1]*). He recom-

mends administering methylprednisolone 40 mg intravenously every 6 h or prednisone 60 mg orally every 6–8 h for 36–48 h with a taper to 60 mg prednisone/d when the FEV_1 approaches 50% of predicted. This dose is held for the next 4 d prior to instituting a taper in 4-d intervals reaching 0 mg in 12 d.

Acute Asthma in Children

There have been several studies evaluating the efficacy of systemic GC therapy in children. As with the studies in adults, the majority have shown systemic GC therapy to be effective in the treatment of acute asthma in children with improvements in PEFR, FEV_1, and PaO_2, decreased frequency of wheezing, or fewer episodes of relapse. Studies evaluating the effect of a single dose of GC in the emergency department setting have uniformly found this therapy superior to placebo in decreasing the number of children who ultimately require admission. Orally administered prednisone in acute asthma in the emergency room setting has also been shown to be effective in decreasing the need for subsequent hospitalization. The administration of iv GC requires placement of an indwelling venous catheter, an often difficult task to perform in an agitated wheezing toddler. Thus, oral GC therapy is an acceptable alternative to iv GC therapy in children. The liquid forms of prednisone (Prelone®, Pediapred®) can be administered to infants and young children who cannot swallow tablets. In addition, the liquid form is very quickly absorbed with peak serum levels occurring at 1 h postdose compared to ~2 h for prednisone tablets.

An important study published in 1987 evaluated whether early intervention with oral steroid therapy during an acute asthma exacerbation in the outpatient setting would prevent further progression of asthma symptoms *(3)*. These investigators administered a short course of high-dose oral prednisone therapy (30–40 mg twice daily for 7 d) or placebo in children with an acute asthma exacerbation. All patients randomized to receive prednisone improved during the week of treatment, with only one relapse noted following discontinuation of prednisone therapy. In contrast, 42% of the patients on placebo developed worsening asthma symptoms requiring rescue intervention. Somewhat surprisingly, a sizable percentage of patients on placebo improved at the same rate as those who received prednisone. Unfortunately, there were no reliable distinguishing characteristics that could have served as predictors of those patients who required GC therapy to prevent worsening of their asthma compared to those who improved spontaneously. Thus, since continued symptoms often lead to emergency care and/or hospitalization, the above study supports the early use of oral steroid therapy for acute exacerbations.

Such issues as the optimal GC dose, the duration of treatment, and the route of administration remain largely empirical and depend largely on the severity of the acute exacerbation. Since orally administered GCs are rapidly absorbed and are usually as effective as iv GC, oral therapy can be used in many cases. Hospitalized children who require high flow rates of oxygen to treat hypoxemia adequately are obvious candidates for iv GC therapy. The NHLBI guidelines recommend administering methylprednisolone (iv or oral), 1–2 mg/kg/dose every 6 h for 24 h and then 1–2 mg/kg/d in divided doses every 8–12 h. The duration of therapy is again left to the discretion of the physician, with the length of treatment dependent on response to therapy. Once oral medications are tolerated, a switch to oral prednisone can be made at a dose of

2 mg/kg/d in two divided doses for an additional 2–4 d followed by a taper to 1 mg/kg/d administered in a single morning dose for an additional 2–4 d prior to stopping. For outpatient management of acute exacerbations, we usually recommend a short course of prednisone, 2 mg/kg/d in two divided doses for 2–3 d followed by a reduction to 1 mg/kg in a single morning dose for an additional 2–3 d.

Efficacy of Oral GC Therapy in the Management of Chronic Asthma

Inhaled GC therapy has allowed the majority of patients with asthma to maintain good control of their disease. When used appropriately, inhaled GC therapy has allowed a significant number of patients with severe asthma to reduce or even discontinue their maintanence oral steroid. Oral GCs are primarily reserved for use in managing acute asthma exacerbations. Unfortunately, a small number of asthma patients continue to require regular use of oral GC therapy despite high-dose inhaled GC and are commonly referred to as steroid-dependent asthmatics. Adequate studies evaluating the efficacy of oral GC therapy over long periods of time are limited. The first and possibly the best study came from the Medical Research Council nearly 40 years ago. This multicentered, randomized, placebo-controlled study showed hydrocortisone to be superior to placebo in several parameters, including fewer relapses, improvement in the physical examination, and exercise tolerance. As expected, all the patients on cortisone developed at least one steroid-associated side effect, the most common being weight gain, followed by hypertension, edema, and cushingoid changes.

Alternate-Day GC Treatment

Given that daily administration of oral GC therapy resulted in multiple adverse effects, investigators began evaluating the effectiveness and adverse effects profile of intermittently administered oral GC therapy (*see* ref. *4*). These pioneering investigators made the important and insightful observation that the therapeutic effects of GCs appeared to persist longer than their metabolic effects. Given this observation, they then attempted several dosage schedules and found that a single morning dose of oral steroid administered every 48 h was the most effective in optimizing asthma care while minimizing the potential for adverse effects. This is a hallmark study, since it set the standard for using alternate-day steroids in the severe asthmatic.

GC and Rate of Response in Chronic Asthma

A number of studies have shown oral GC therapy to improve symptoms and relieve airflow obstruction in chronic asthma. Improvement is seen within the first 48 h with peak improvement noted by 8 d of therapy. The vast majority of asthmatics should display a significant improvement in their pulmonary function within 7–10 d of high-dose GC therapy. Patients who fail to respond after 10 d of high-dose GC therapy can be termed clinically steroid-resistant and may be candidates for alternative asthma therapy.

Management of Steroid-Dependent Asthma

There are several management issues to consider when caring for patients with steroid-dependent asthma. First, all other asthma therapy should be optimized, including inhaled GC, long-acting theophylline, and judicious use of β-agonists. Second, the diagnosis of asthma should be firmly established. Third, such factors as inappropriate

inhalation technique and poor compliance with asthma medications, environmental control (in atopic patients), gastroesophageal reflux, and sinusitis can contribute to poor asthma control and should be evaluated for, and if present, adequately treated. Finally, given the inevitable development of potentially severe steroid-associated adverse effects, every attempt should be made to determine the lowest possible oral steroid dose and, if at all possible, administered on alternate days.

To determine the need for, and lowest possible required oral GC dose (i.e., steroid threshold), a gradual taper of the GC should be attempted with close monitoring of the patient's symptoms (nocturnal episodes of wheezing/shortness of breath, degree of exercise-induced bronchospasm, frequency of inhaled bronchodilator use) and pulmonary function (PEFR monitoring, spirometry). The daily oral GC dose can be tapered by 5 mg/wk until 20 mg on alternate days is reached or until breakthrough asthma symptoms or declining pulmonary function is observed. Since most of these individuals will be adrenally suppressed, the taper is then slowed with weekly reductions in the oral GC dose by 2.5 mg every other week with periodic measurement of AM cortisol levels to assess adrenal recovery. If during the glucocorticoid taper, the patient develops increasing asthma symptoms and/or diminished pulmonary function, a beneficial steroid effect is documented and a threshold dose is defined. If the prednisone (or its equivalent) threshold dose is >20 mg in adults (or >10 mg in children) on alternate days, consideration for alternative asthma medications may be indicated.

ADVERSE EFFECTS OF SYSTEMIC GC THERAPY

Since all nucleated cells in the body have a common glucocorticoid receptor, all are potentially affected by GC therapy, and thus susceptible to the development of untoward effects. These effects can occur immediately (i.e., metabolic effects) or can develop insidiously over several months to years (i.e., osteoporosis and cataracts). In addition, some adverse effects are limited to children (growth suppression), whereas others appear to require interaction with other drugs (peptic ulcer disease). Most adverse effects occur in a dose-dependent and duration of treatment manner, although this has not been uniformly noted. Table 3 lists many of the common adverse effects associated with chronic GC use. The following discussion will focus on those adverse effects that are especially important for the clinician caring for the chronically GC-dependent asthmatic. Failure to recognize and adequately treat these problems could result in severe morbidity.

Osteoporosis

Osteoporosis, a significant and common adverse effect, is often overlooked secondary to its insidious onset and the insensitivity of conventional diagnostic methods. All patients who have been on >7.5 mg prednisone (or equivalent) daily for at least 6 mo are at risk for developing osteoporosis. Although the etiology of GC-induced osteoporosis is complex, decreased calcium absorption from the intestinal tract and decreased renal reabsorption are major factors. In addition, GCs inhibit osteoblast function, resulting in decreased bone growth while stimulating osteoclast activity, which results in bone resorption. Trabecular bone (ribs, vertebrae) appears to be more sensitive to the effects of GCs than cortical bone. Factors that increase the likelihood of the de-

Table 3
Adverse Effects Associated with Systemic GC Use

Cardiovascular effects
Hypertension
Dermatolic effects
Dermal thinning/increased skin fragility
Acne
Endocrinologic effects
Adrenal suppression
Growth suppression and delayed sexual maturation in children
Weight gain, development of cushingoid habitus
Diabetes mellitus
Hematologic effects
Lymphopenia, neutrophilia
Immunologic effects:
Diminished immunoglobulin levels
Loss of delayed-type hypersensitivity (DTH)
Potential for increased risk of infection
Metabolic effects:
Hypokalemia, hyperglycemia, hyperlipidemia
Musculoskeletal effects
Osteoporosis/vertebral compression fractures
Aseptic necrosis of bone (hips, shoulders, knees)
Myopathy (acute and chronic)
Ophthalmologic effects
Cataracts, glaucoma
Psychologic/neurologic effects
Mood swings, psychosis
Steroid withdrawl syndrome
Pseudo-tumor cerebri

velopment of osteoporosis include inactivity, sex hormone deficiency, a diet deficient in calcium, and concurrent use of drugs, such as furosemide, anticonvulsants, and excessive thyroid hormone replacement.

Because demineralization of bone is not detectable on conventional radiographs until a significant degree of bone mineral density is lost, the diagnosis of osteoporosis is best made by documenting decreased bone mineral density utilizing a bone densitometer. Further assessment of osteoporosis in the steroid-dependent asthmatic includes 24-h urine calcium measurement, which provides useful information regarding the extent of GC-induced renal calcium loss. Biochemical markers, such as serum osteocalcin (a marker of osteoblast activity) and urinary hydroxyproline (a marker of bone resoption), may eventually become routinely followed, but at present, insufficient information is available to apply these markers for general clinical practice.

Treatment of osteoporosis, as is the case for all steroid-induced adverse effects, consists of attempting to decrease the oral GC dose and/or frequency, increasing calcium intake to 1000–1500 mg of elemental calcium/d supplemented with at least 400 IU/d of

Table 4
Management of GC-Induced Osteoporosis

Minimize oral GC dose to ≤20 mg in adults and ≤10 mg in children (prednisone or equivalent) on alternate days
Increase calcium (Ca^{2+}) intake to 1000–1500 mg elemental Ca^{2+}/d
Increase dietary calcium intake by eating foods high in calcium
Consider additonal calcium in the form of a calcium supplement,[a] such as
Calcium carbonate (40% elemental Ca^{2+})
Oscal® 500 contains 500 mg elemental Ca^{2+}/tablet
Tums® contain 200 mg elemental Ca^{2+}/chewable tablet
Calcium citrate (21% elemental Ca^{2+})
Citrical® 950 contains 200 mg elemental Ca^{2+}
Calcium gluconate (9% elemental Ca^{2+})
Vitamin D supplementation—400 IU/d
Increase physical activity
Gravity-dependent activities, such as walking/low impact aerobics, are most effective
Avoid heavy lifting, contact sports, high impact aerobics
Consider use of a diuretic, such as hydrochlorothiazide, if 24-hr urinary Ca^{2+} is > 400 mg
Other agents used for severe osteoporosis
Calcitonin
Bisphosphonates
Calcitriol
Sodium fluoride
Estrogen (indicated for postmenopausal osteoporosis)

[a]Note that Ca^{2+} is in the form of a salt; thus, the amount of elemental Ca^{2+} will be a percentage of the total weight of the tablet unless the label specifies the amount of elemental Ca^{2+} per tablet.

vitamin D (Table 4), and increasing physical activity (especially gravity-dependent activities, such as walking). Avoidance of activities, such as heavy lifting, high impact aerobics, and contact sports (football, wrestling), is recommended, since these activities can result in compression fractures of the vertebral bodies (bending, lifting, contact sports) in addition to fractures of the long bones (contact sports). If hypercalcuria is present, hydrochlorothiazide can be used alone or in combination with a potassium-sparing diuretic. Patients with severe osteoporosis may require treatment with a remittive medication and should be managed with the assistance of a bone specialist.

Myopathy

Two distinct types of myopathy can occur with systemic GC therapy. An acute, severe myopathy associated with short-term high-dose parenteral GC therapy has been reported in patients hospitalized with severe asthma exacerbations. This presentation is rare, and the etiology unclear, but several conditions appear to contribute, including intubation with mechanical ventilation, concurrent use of muscle relaxant therapy, and possible accelerated disuse atrophy. Affected patients often have markedly elevated serum creatine phosphokinase (CPK) levels and diffuse necrosis of skeletal muscle on

biopsy. Recovery begins after GC withdrawal, but more than 6 mo may be required for complete recovery.

More commonly encountered is the insidious development of proximal muscle atrophy in chronically GC-dependent patients. As with the other previously described adverse effects, those patients receiving daily steroids or large alternate-day doses for prolonged periods are at greatest risk. Isokinetic muscle testing of hip flexor strength appears to be the most sensitive and objective measure of proximal muscle weakness. Enzymes of muscle origin, such as CPK, aldolase, and lactate dehydrogenase (LDH), are almost never elevated, and biopsy of affected muscle reveals atrophy of the type IIb fast-twitch glycolytic fibers. To correct and/or prevent GC-induced myopathy, every attempt should be made to taper the GC dose, and a program designed to improve muscle strength initiated. As was noted with the acute form, more than 6 mo of rehabilitation may be required before normal muscle strength is attained.

Cataracts

Posterior subcapsular cataracts (PSC) are a well-described complication of chronic glucocorticoid use with a prevalence rate of up to 29%. The mechanism(s) involved in their development is not clear, but may involve disturbances of carbohydrate metabolism or "dehydration" of the lens. GC-induced cataracts are often small, but can at times significantly affect visual acuity, requiring surgical intervention. Even though the development of cataracts appears to be related to the daily dose, cumulative dose, and the duration of treatment, there is a significant degree of variability with respect to individual susceptibility to cataract formation. It is unknown whether GC dose reduction will result in regression or disappearance of the cataract, although some studies suggest that if recognized early, regression can occur. A yearly ophthalmologic exam to evaluate for the presence of cataracts is recommended for all patients receiving maintenance oral GC therapy.

Growth Suppression

Growth suppression is the steroid-associated adverse effect that causes the most concern for clinicians caring for children. Regular daily therapy, frequent short courses, or high-dose alternate-day GC therapy often results in suppression of linear growth. Doses of prednisone as small as 0.1 mg/kg administered daily for as short a period of time as 3 mo has resulted in significant suppression of linear growth. When the GC is administered on alternate days, the degree of suppression is usually less, but significant growth suppression can still occur. The mechanism(s) involved in linear growth suppression remain poorly understood, but may involve suppression of growth hormone production, somatomedin activity, and/or direct inhibitory effects on bone and connective tissue. Complicating the issue of GC-induced linear growth suppression is the finding that asthma itself can impair growth. This is a significant issue, especially as it pertains to whether chronic inhaled GC therapy is associated with growth suppression (*see Adverse Effects of Inhaled GC Therapy*). Since daily or high-dose alternate-day GC therapy for extended periods of time can result in permanent growth retardation, every effort should be made to decrease the amount of oral GC to <20 mg on alternate days. If the child's oral GC dose cannot be tapered to ≤20 mg on alternate days, recombinant

growth hormone (GH) therapy can be utilized. GH has been shown to increase linear growth in children on chronic oral GC therapy, but the response to GH is dependent on the dose of GC administered; the higher the daily dose of prednisone, the less effective GH therapy is likely to be.

Adrenal Insufficiency

Patients who are adrenally suppressed as a consequence of oral chronic glucocorticoid therapy are at risk of developing acute adrenal insufficiency at times of acute stress, such as surgical procedures, gastroenteritis associated with diarrhea and emesis, or trauma. Patients who develop acute adrenal insufficiency can present with dehydration, shock, electrolyte abnormalities, severe abdominal pain, and lethargy out of proportion to the severity of their presenting illness. This is a medical emergency that requires prompt diagnosis and rapid treatment with iv hydrocortisone (2 mg/kg initially followed by 1.5 mg/kg every 6 h until stabilization is achieved and oral therapy is tolerated) as well as vigorous fluid replacement with normal saline if dehydration and hypotension are present. All patients on chronic high-dose GC therapy should be considered adrenally suppressed and should wear a medical alert bracelet that identifies them as being at risk for acute adrenal insufficiency. All adrenally suppressed individuals should be given hydrocortisone at the time of any surgical procedure (1–2 mg/kg) and every 6 h thereafter for the next 24–48 h with a switch to their usual oral GC dose when oral medications are tolerated. The same recommendations are to be followed at other times of acute stress. Complete recovery from adrenal suppression can take from 6 mo to 1 yr after cessation of long-term GC use. Thus, all patients with a history of chronic GC use should be considered adrenally suppressed, and should be managed as such for up to 1 yr following cessation or significant reduction of oral GC therapy.

Other Adverse Effects

Other common adverse effects of chronic GC therapy include increased appetite with weight gain and the development of a Cushingoid habitus, consisting of a moon facies, buffalo hump, central obesity with wasting of the extremities, atrophy of the skin with the development of striae, and hirsutism. Psychologic disturbances from increased emotional lability to frank psychosis can occur, as well as hypertension, peptic ulcer disease, atherosclerosis, aseptic necrosis of bone, and diabetes mellitus. Chronic GC use can also result in immunologic attenuation with loss of delayed-type hypersensitivity, diminished IgG levels without change in functional antibody response, potential for reactivation of latent tuberculosis infection, and possible increased risk for infection, especially the development of severe varicella.

INHALED GC THERAPY

Effective forms of inhaled GC were first introduced in the early 1970s with the development of drugs and delivery devices that provided optimal topical to systemic potency. In other words, by effectively delivering a small quantitiy of a potent GC directly into the airway, inhaled GC therapy maximizes the beneficial effects while minimizing the systemic effects associated with chronic GC use. Even though these medications have been available for over 20 years, their use, especially in pediatric patients, has been

- Topical GCs are now considered first line therapy in moderate asthmatics.
- Low doses of 250–500 μg/d are recommended as initial starting amounts for moderate asthmatics but doses can be increased (800–1000 μg/d) for more severely ill patients, and some require >1000 μg/d.
- Some systemic side effects can occur with the use of topical corticosteroids, so the dose should be kept as low as possible to maintain control. The significance of these side effects has not been established.

limited to those patients with severe asthma. As our understanding of asthma has changed, with increasing emphasis on airway inflammation even in mild asthma, inhaled GCs are now considered first-line therapy in moderate asthma.

Efficacy of Inhaled GCs

As mentioned previously, BHR is a characteristic finding in asthma. The degree of BHR correlates with asthma severity; the greater the BHR, the more severe the asthma. In addition, BHR is in some way related to airway inflammation. Thus, inhaled anti-inflammatory medications should be effective in decreasing BHR. Studies evaluating the effect of inhaled GC therapy in asthma have consistently demonstrated a favorable effect on BHR in both adults and children. In fact, inhaled GCs may be superior to oral GCs in their ability to diminish nonspecific BHR. Decreases in BHR of two- to sevenfold have been reported within 2–6 wk of instituting inhaled GC therapy. Of significance, the decreases in BHR have been associated with fewer asthma symptoms, improved pulmonary function (PEF and FEV_1), less need for supplemental β-agonist use, and fewer exacerbations requiring oral GC therapy.

Recent studies utilizing bronchoscopy and bronchial biopsy have demonstrated reductions in airway inflammation at several levels. First, inhaled GC therapy has resulted in significant reductions in the number of inflammatory cells, the number of cells expressing proinflammatory cytokine mRNA, and the number of activated helper T-lymphocytes in the bronchoalveolar lavage fluid or airway submucosa. Second, the airway epithelium "heals" following the long-term administration of inhaled GC therapy. Third, inhaled GC therapy has recently been shown to be effective in decreasing the amount of Type III collagen depostion within the basement membrane. Basement membrane thickening is a characteristic finding in chronic asthma, and although its role in the pathophysiology of asthma is unclear, it may contribute to the development of chronic and potentially irreversible airflow obstruction. Thus, chronic administration of inhaled GC therapy results in reductions in BHR, symptoms, and need for supplemental β agonist use. Associated with this is improved pulmonary function and suppression of the inflammatory response characteristic of asthma.

When to Use Inhaled GCs

A recent report from the NHLBI, entitiled International Consensus Report on Diagnosis and Management of Asthma, recommends a stepwise approach to asthma pharmacotherapy. The first step encompasses mild asthma. First-line therapy in this group is intermittent β agonist use for symptoms and prior to exercise. Those patients with mild

asthma have brief, infrequent episodes of bronchospasm (<1–2 times/wk), <1–2 episodes of nocturnal symptoms/mo, and PEFR or FEV_1 values of >80% of predicted. Inhaled GC therapy is recommended in increasing doses for steps 2 and 3, which encompass moderate asthma, and for step 4, which encompasses severe asthma. Patients with moderate asthma have, by definition, more frequent asthma symptoms, including >1–2 episodes of bronchospasm/wk, >1–2 episodes of nocturnal symptoms/mo, and PEFR or FEV_1 60–80% of predicted. Inhaled GC at doses of 250–500 μg/d are recommended as an initial starting dose at step 2 with an increase to 400–750 μg/d if necessary. If the patient continues to have symptoms, or is in the moderately severe catagory (step 3), higher-dose inhaled GC (800–1000 μg/d) is recommended in addition to sustained-release theophylline, and use of short-acting β agonist as needed. Patients who have continuous asthma symptoms and frequent nocturnal awakening with symptoms, and are physically limited by asthma symptoms are considered to have severe asthma and have PEFR or FEV_1 values of <60% of predicted. High-dose inhaled GC therapy (>1000 μg/d) is recommended, as is theophylline, intermittent β agonist use, and chronic oral GC therapy if indicated.

Should Inhaled Glucocorticoids Be First-Line Therapy in Mild Asthma?

Whether inhaled GC therapy should be first-line therapy in mild asthma remains a topic of debate. Those that favor the use of inhaled GC therapy in mild asthma argue that since this medication reduces airway inflammation, BHR, and need for supplemental β agonist therapy, it should be used in all patients with asthma. Given that inhaled GC therapy is not without the potential for adverse effects, and that adequate long-term studies evaluating bone demineralization and growth delay (in children) have yet to be completed, others argue that their use be reserved for those with more frequent symptoms, i.e., those with moderate to severe asthma.

Two recent studies, one in children and the other in adults, evaluated the efficacy and adverse effects of budesonide, a potent inhaled GC not yet available in the United States, in mild asthma. Both studies found budesonide therapy to be effective in decreasing asthma symptoms, supplemental β agonist use, and improving pulmonary function with few adverse effects noted. The pediatric study found doses of budesonide of ≤400 μg/d not associated with growth suppression over a 3.5-yr period *(5)*. Of concern, higher doses of budesonide resulted in suppression of linear growth compared to children with asthma who were not on inhaled GC. Another interesting finding from this study was the observation that the longer the child had asthma prior to instituting budesonide therapy, the less significant the improvement in pulmonary function following initiation of budesonide therapy. A similar result was seen in the study of adult asthmatics *(6)*. In this study, one-half of the study population was treated with budesonide for 2 yr and the other was treated with regularly administered terbutaline, a β-agonist. Not surprisingly, the group on budesonide had a significant improvement in their pulmonary function, whereas those on terbutaline actually had a gradual worsening. The study was then extended for an additional year, at which time those who were on terbutaline received budesonide, whereas those initially on budesonide either received a smaller dose (400 μg/d compared to 1200 μg/d) or were administered placebo. The pulmonary function of those asthmatics who were placed on budesonide after 2 yr of placebo therapy improved, but not to the same extent as those patients who received

budesonide at the time of diagnosis. The results from both studies suggest that the longer the time from the initiation of symptoms and subsequent treatment with inhaled GC, the less effective the therapy will be possibly secondary to the development of some degree of irreversible airflow obstruction.

Types of Inhaled GC

There are currently three inhaled GC preparations available for use in the United States: beclomethasone dipropionate (BDP), marketed as Vanceril® or Beclovent®, both of which deliver 42 μg/actuation, triamcinolide acetonide (TAA), marketed as Azmacort®, which delivers 200 μg from the cannister but only 100 μg/inhalation from the built-in spacer device, and flunisolide (FLN), marketed as Aerobid®, which delivers 250 μg/actuation (Table 5). Budesonide and fluticasone propionate are "second"-generation inhaled GCs, which appear to have greater topical-to-systemic potencies. Budesonide and fluticasone are not yet available for use in the United States, but should be approved for use in the near future. Few if any studies have attempted to compare the clinical efficacy of the available inhaled GCs. As a result, we consider each GC to be equipotent on a microgram-to-microgram basis. With that in mind, the differences among the three products come from the amount of drug delivered per actuation. Thus, BDP delivers the least amount and is often used for those asthmatics requiring low-dose therapy. TAA delivers an intermediate amount and is often used in asthmatics requiring intermediate doses. FLN, by virtue of its ability to deliver the greatest amount per actuation, is often used in severe asthmatics on high-dose inhaled GC therapy.

Just as there have been few studies comparing the bioequivalence of the various inhaled GC compounds, few studies have compared the bioequivalence of inhaled to oral GC. Inhaled budesonide at a dose of 2000 μg/d has been found to be as effective as ~40 mg of daily prednisone in terms of improving asthma control, whereas 1840 μg/d were equivalent to ≥15 mg/d of prednisone in terms of systemic effects (suppression of cortisol and circulating eosinophil counts). This observation reiterates two important points: first, that inhaled GC, have a higher topical-to-systemic ratio, and second, that high-dose inhaled GC therapy can result in significant systemic effects.

Dose/Frequency of Use

The dose of inhaled GC chosen is largely dependent on the clinical situation. The more severe or poorly controlled the asthma, the higher the initial dose. We often begin with high-dose inhaled GC therapy in an attempt to optimize pulmonary function and clinical symptoms. Once the patient's asthma is improved, we then taper the dose following clinical symptoms and pulmonary function closely. The ideal inhaled steroid dose should be large enough to control asthma symptoms, yet small enough to avoid the potential for adverse systemic effects. Inhaled GCs are frequently administered three to four times daily, although flunisolide has been marketed to be administered twice daily. Studies in patients with moderate to severe asthma that have evaluated the effectiveness of twice daily compared to four times daily therapy (same total daily dose administered) have demonstrated enhanced efficacy when the GC is administered four times daily. In contrast, studies in mild asthmatics have failed to show improved efficacy of the more frequently administered drug. Thus, when deciding on how often to administer an inhaled GC, one must consider the clinical situation, keeping in mind that compliance

Table 5
Maximum Recommended Inhaled GC Doses

	Adults			*Children*		
Glucocorticoid	μg/ *inhalation*	*Inhalations/d*	μg/d	μg/ *inhalation*	μg/d	*Inhalations/d*
Beclomethasone Dipropionate (Beclovent®, Vanceril®)	42	20	0.84	42	10	0.42
Triamcinolone Acetonide (Azmacort®)	100[a]	16	1.60	100*	12	1.20
Flunisolide (Aerobid®)	250	8	2.00	250	4	1.00

[a]200 μg delivered/actuation, but 100 μg retained within built-in spacer device.

rates decrease significantly when the drug is administered more than twice daily. If the patient is poorly controlled, high-dose GC therapy should be administered four times daily with the patient's dose (both frequency of administration and amount administered) decreased as asthma control improves.

Adverse Effects of Inhaled GC Therapy

The development of adverse effects is in large part dependent on the dose and the frequency with which the inhaled GC is given. High doses administered frequently (i.e., four times daily) are most likely to result in an increase in both local and systemic adverse effects. The most commonly encountered adverse effects from inhaled GC therapy are local and consist of oral candidiasis (thrush) and dysphonia (hoarse voice). Thrush is thought to occur as a result of local immunosuppression, whereas dysphonia occurs as result of vocal cord muscle myopathy. These effects are dose-dependent and are most common in individuals on high-dose inhaled and oral GC therapy. The incidence of these local effects can be greatly minimized by using a spacer device that reduces the oropharyngeal deposition of the drug. In addition, mouth rinsing with water further reduces the amount of drug left in the oropharynx and should be strongly encouraged.

Although the risk for developing systemic adverse effects is much smaller for inhaled compared to oral GC therapy, the potential for toxicity remains. Several systemic effects have been reported and include suppression of the hypothalamic pituitary axis (HPA), weight gain, growth suppression, cataracts, dermal thinning, and osteoporosis. Although this area remains controversial, most clinicians would agree that high doses (>1000 μg/d) are most likely to be associated with the greatest risk for adverse effects. The adverse effects that are of greatest concern include growth suppression in children, HPA axis suppression, and the insidious development of osteoporosis. At present, many questions remain regarding the risk for adverse effects. Studies designed to address these concerns are in progress and until a clear consensus emerges, it is prudent to use

the lowest tolerated inhaled GC dose and to keep in mind that systemic effects can occur in those patients who require high-dose therapy for adequate asthma control.

SUMMARY

GC therapy has become an important pharmacologic modality in asthma therapy. Although potent and generally effective, systemic GCs are not without risks for development of serious adverse effects, especially when used in high doses and for prolonged periods of time. Fortunately, inhaled GC products have been developed that greatly minimize the systemic adverse effects while retaining beneficial airway effects. Many previously steroid-dependent asthmatics have been tapered off oral GC following institution of inhaled GC therapy. As with oral GC therapy, high-dose inhaled GC therapy has been associated with systemic adverse effects, and it is still unclear whether long-term administration of inhaled GC will result in growth suppression and osteoporosis. Thus, the clinician must balance the therapeutic effects of both inhaled and oral GC with their risks for adverse effects. Obviously, using the lowest possible effective GC dose as well as maximizing other therapeutic modalities can be means by which this goal is achieved. Early recognition and appropriate management are other methods to minimize GC-induced adverse effects. With the principles set forth, specifically maximization of therapy, early recognition of breakthrough symptoms, and appropriate management of adverse effects, the potential severe complications of GC therapy can be minimized.

ACKNOWLEDGMENTS

This work was supported in part by the National Institutes of Health, Heart, Lung, and Blood Institute, grants HL-36577, RR00051. S. J. Szefler is the Mary Wohlberg & Herman Lambert Chair in Pharmacokinetics.

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22 Environmental Control for Allergic Disease

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CONTENTS

INTRODUCTION

The air we breathe contains a broad spectrum of airborne allergens and irritants that are derived from a variety of organic and inorganic sources. These airborne substances are capable of triggering symptoms of asthma, bronchitis, and rhinoconjunctivitis. Although outdoor allergens and pollutants receive a great deal of attention, the average American spends 93% of his or her time indoors. Therefore, control of the indoor environment is likely to have a significant impact on the health of patients who are sensitive to indoor airborne substances.

Even patients who do not have allergic disease may develop significant respiratory tract and ocular symptoms when exposed to high concentrations of particulate matter or volatile substances capable of producing an irritant response when contacting a mucosal surface. However, since the respiratory and conjunctival surfaces of allergic and asthmatic patients are often chronically inflamed, excessive mucous production, nasal congestion, sneezing attacks, nasal and ocular itching, and bronchoconstriction occur at relatively low concentrations of airborne irritants. Furthermore, the threshold for allergen to trigger symptoms in allergic, sensitized individuals can be exceedingly low. (For example, exposure to an environment containing as little as 10 μg of dust mite antigen/g of settled house dust can result in an asthma attack, and even lower concentrations of the antigen may lead to developing allergic sensitivity in susceptible patients.)

Therefore, it is important that measures be taken to control the environment of the allergic patient. The potential benefits of minimizing allergen and irritant exposure in-

From: *Allergic Diseases: Diagnosis and Treatment*
Edited by P. Lieberman and J. Anderson Humana Press Inc., Totowa, NJ

clude lower symptom frequency and severity, lower medication requirements, and decreased risk of allergic sensitization. A variety of low-cost, safe, and simple methods to reduce exposure to common indoor allergens and irritants will be discussed in this chapter.

ALLERGEN CONTROL MEASURES

A variety of biologic sources are capable of generating airborne proteins that can lead to allergic sensitization (Table 1). Since extremely small amounts of these proteins can trigger symptoms in sensitized subjects, environmental control measures are an important method of treatment for allergic patients.

Dust Mite Allergy

Dust mites are a clinically important indoor allergen. Several studies of skin tests in allergic patients with asthma suggest that 50–80% are dust mite sensitive. Mites are also one of the most common causes of allergic rhinitis.

Dust mites are small (0.3 mm long) arachnids whose common food sources include feathers, fungi, and human skin scales (thus their genus name is *Dermatophagoides*). The proteins that are most likely to induce allergic symptoms are present in high concentrations in mite feces and are also found in mite bodies. Environmental factors that favor dust mite growth and reproduction include an adequate food source, relative humidity of 60–75%, and temperatures of 65–85°F. Favorable conditions for mite growth are often present in mattresses, carpets, upholstered furniture, and basements of homes. It is interesting to note that homes built at high altitudes tend to have very few mites (probably owing to low humidity and oxygen levels). Finally, since dust mite antigen is present in particles that are relatively large in size, the allergen becomes airborne only with mechanical disturbance of settled dust and resettles within minutes.

Several studies show that if dust mite-allergic patients with asthma are moved to environments with relatively low dust mite exposure, their symptoms of asthma will improve. The fact that dust mite avoidance is of clinical benefit combined with the knowledge of factors that influence the location and growth of dust mites provide the basis for recommendations to devise a plan to control exposure levels to this allergen (Table 2).

Dust mites appear to be exquisitely sensitive to changes in humidity. In fact, many species of dust mite cannot survive at < 40–50% relative humidity. Therefore, lowering the humidity in some homes can be an effective measure to decrease dust mite exposure.

The total elimination of dust mite would be impractical, expensive, and may not be necessary to improve symptoms in sensitive patients. A more practical approach, and one that is relatively inexpensive, is to focus on controlling levels of dust mite antigen in locations within the home that are most likely to result in significant respiratory exposure of the patient.

Dust samples collected from mattresses contain high levels of dust mite compared to most other locations in the home. This may be secondary to the fact that mattresses tend to hold moisture and contain large amounts of human skin scales, which serve as a food source for the mites. The level of exposure to mattress dust is also significant since patients spend approx 8 h each day breathing air that has been drawn across the mattress

Table 1
Common Sources of Household Allergens

Dust mites
Household pets: cats, dogs, rodents, rabbits
Indoor molds: *Penicillium*, *Aspergillus*, and *Cladosporium* species
Cockroaches
Outdoor allergens: pollens and molds that gain access to home
Wild rodents: typically mice or rats
Furniture component: Horse hair or Kapok stuffed articles
Food: Aerosolized proteins from seafood and possibly other allergenic foods can trigger respiratory symptoms

Table 2
Dust Mite Environmental Control Recommendations

Universal recommendations
Feather containing pillows and comforters must be removed from the bed or covered with an allergen-proof slipcase
Mattresses and box springs should be encased in a zippered allergen-proof slip cover; slipcovers or vinyl waterbed surfaces should be wiped with a damp cloth every 1–2 wk
All bedding (including pillows if not encased in a slipcover) should be washed every 1–2 wk in hot (>130°F) water
Carpeting and upholstered furniture should be vacuumed weekly (preferably by a nonallergic individual and a vacuum equipped with a double bag or high-efficiency filter system)
Heavily dust laden articles (stuffed toys, old upholstered furniture) should be removed from the bedroom
Masks should be worn if allergic individuals need to vacuum or work in dusty areas
Aim for a relative humidity in the home of < 50%
Recommendations for severe symptoms or highly motivated patients
Carpeting should be removed from the bedroom and replaced with linoleum or polished wood
Fabric drapes and upholstered furniture should be removed from the bedroom and replaced with vinyl or metal blinds, and vinyl, leather, or wood furniture
Acaricides should be used on carpets every 6–8 wk
Aim for a relative humidity in the home of < 40%

surface. This has led to recommendations that mattress and box springs should be encased in zippered vinyl slipcovers that can be dusted with a damp cloth on a weekly basis. Some slipcovers are available that have a cloth backing to minimize the discomfort of sleeping on vinyl. Waterbed mattresses with vinyl surfaces are not significant reservoirs for dust mites. However, damp cloth dusting of the surface of the waterbed is recommended on a weekly basis.

Similarly, high exposure to dust mite antigen can be attributed to close contact to other bedding, including pillows, sheets, blankets, bedspreads, and mattress pads. How-

ever, most of these items can be laundered, and this is recommended every 1–2 wk. It appears that hot water washing is most effective in lowering the numbers of dust mites in bedding. Therefore, all patients should be reminded to use only the "hot water cycle" when accomplishing this task. Some bedding, including feather-filled pillows and comforters, cannot be washed. Since feathers are a favored food source for mites, these items should be removed from the bed. Although vinyl encasements are an alternative for feather pillows, many patients find the vinyl case uncomfortable and prefer to change to a nonfeather pillow.

On being told that they are allergic to dust mites, patients commonly react by attempting to rid their homes of the allergen by intensive vacuuming and dusting. Most studies show that these efforts are not likely to be beneficial. In fact, most vacuum devices tend to disperse dust mite allergens into the air, resulting in significant allergen exposure during vacuuming. Although routine vacuuming is necessary to prevent the accumulation of excessive surface dust, the best recommendation is to have other individuals perform the necessary vacuuming or have the allergic patient wear a mask when doing so. Some vacuum cleaners can be equipped with "double-thickness" filter bags or high efficiency particulate air (HEPA) filters, which do decrease the dispersion of airborne mite antigen while vacuuming. These devices can be recommended for allergic patients, although some of these vacuum models are expensive.

Floor coverings, such as carpets, are clearly a reservoir for dust mites as well as other allergens compared to mite-impermeable surfaces, such as linoleum, tile, or polished hardwood flooring. Carpeting that is placed on damp surfaces, such as concrete flooring, tends to have an exceptionally high allergen content. The removal of carpeting from the bedroom should be considered for patients with a high degree of sensitivity to mites, severe allergic symptoms, or those whose symptoms have failed to respond to other measures.

A proposed alternative approach to carpet removal is the treatment of carpeting with agents that kill dust mites or denature dust mite antigen. Several acaricides (chemical agents that kill dust mites) have been studied. Benzyl benzoate is a commercially available acaricide powder that is to be sprinkled onto and worked into the carpet by vigorous brushing. Solutions of tannic acid have also been applied to carpeting in attempts to denature mite antigen protein. The degree to which these agents provide clinical improvement in allergic patients has not been established.

Finally, a carefully performed clinical history may point to the presence of significant allergen exposure via mite-laden articles, such as stuffed toys, upholstered furniture (particularly in dark, damp living areas), or in certain other areas of the home. Patients often provide a convincing scenario of rapid-onset sneezing episodes or asthma symptom onset within minutes of exposure in these environments. If these factors can be identified, simple avoidance behaviors can be applied. In addition, stuffed toys or other small articles can be intermittently placed in the freezer for 24 h, which will kill dust mites.

Environmental Control for Household Pet Allergy

Another group of clinically important environmental allergens is the airborne protein derived from household pets. Nearly half of the households in the United States have a cat or dog. Astonishingly, one-third of all pet-allergic individuals have the offending an-

imal in their home. A variety of household pets, including mice, guinea pigs, hamsters, rabbits, and other fur-bearing animals, are also potentially allergenic. Although dramatic improvement in allergic symptoms can be achieved by removing pets from the home, many patients do not accept this treatment strategy. Although environmental control measures are similar for all fur-bearing animals, the focus of the following discussion will be on the most common household pets in the US, cats and dogs.

Cat Allergy

Cats secrete a protein antigen (*Fel d* I) derived from their skin and saliva, which is responsible for inducing the majority of symptoms in cat-allergic patients. The protein becomes airborne after the secretions dry on the cat's fur. A fraction of this antigen, which is present in small particles, may remain airborne for several hours. The physical characteristics of these small particles allow them to distribute themselves to areas of the home that are distant to where the cat is "kept" and allow the antigen to "stick" to household surfaces and clothing. Several studies have shown that amounts of *Fel d* I that are sufficient to produce symptoms can be present in homes and other buildings (such as schools and hospitals) where cats have never been present. Presumably, this occurs from transfer of antigen that adheres to the clothing of cat owners to other surfaces outside the home.

It is important to note that even when a cat is removed from the home, it may take many months for clinical improvement to occur. Studies show that there is a gradual decline in *Fel d* I after the cat is removed and that even 6 months later, some homes had high concentrations of the protein recovered from household dust samples. It is believed that this is owing to allergen that is adherent to surfaces and present in reservoirs, such as carpeting, mattresses, and furniture. Therefore, it may be important for patients who have removed the cat to institute aggressive cleaning measures, such as washing walls, steam cleaning carpeting, removing likely reservoirs, and increasing fresh air exchange in the home. One study suggests that these cleaning methods result in more rapid decline of cat allergen levels and therefore more rapid clinical improvement in patients can be expected. Since a significant proportion of cat owners refuse to remove the cat from the home, alternative methods that focus on "treating the cat" or "removing" accumulated antigen while the cat is still in the home have been proposed (Table 3). Several studies have suggested that washing cats with tap water on a weekly basis may diminish the amount of allergen that becomes airborne and eventually distributes throughout the home. A recent study concluded that this method of washing the cat is ineffective. It may be that more frequent washing or the use of detergents or allergen-denaturing shampoos may improve this seemingly "logical" approach to cat allergy. However, further studies are required before this approach can be routinely recommended. In addition, a number of commercial products are available that are designed to spray onto or rub into the cat's fur. The clinical effectiveness of these products has not been established.

A practice that has been recommended by some veterinarians has been to medicate the cat with subtherapeutic doses of an animal tranquilizer called acepromazine. The rationale for this approach is to diminish the amount of *Fel d* I that the animal produces. Such an effect was not apparent in a recent placebo-controlled study, and this approach to cat allergy cannot be recommended.

Table 3
Household Pet Environmental Control Recommendations, Based on Cat Studies

If the animal can be removed from the home
Remove the animal as soon as possible
Walls and other impermeable surfaces throughout the home should be wiped with a damp cloth (a tannic acid or other allergen-denaturing solution can be used on appropriate surfaces
Heavily "animal contaminated" carpeting or upholstered furniture should be removed if possible; less contaminated areas should be thoroughly vacuumed or steam cleaned
If the animal cannot be removed from the home
The animal should be confined to areas of the home as remote as possible from the allergic patient's bedroom or areas where the patient is frequently present
Direct contact with the animal is strongly discouraged
Bedroom carpeting should be removed; linoleum, tile, or polished wood floors are recommended
An area air cleaner with an HEPA filter may be effective in uncarpeted rooms
The patient should avoid close contact with clothing or furniture frequently in direct contact with the animal
Cages and urine-contaminated material should not be cleaned by the allergic individual, and direct contact with the animal bedding material should be avoided

Restricting the cat to certain areas of the home may be helpful. Certainly, designating the bedroom as a "cat-free" environment at all times is a logical recommendation. However, the presence of the allergen on small particles makes significant exposure likely even in the areas of the home that are most remote from the living quarters of the cat. With this in mind, the use of room air cleaners with HEPA filters may provide a mechanism to clear airborne allergen in a relatively small area, such as a bedroom. This approach should decrease the total daily allergen exposure, but an evaluation of the clinical effectiveness of air filtration and restricting the living area of the cat awaits scientific study.

All cat-allergic subjects should be told to avoid direct contact with the animal, and also to avoid furniture and other surfaces with which the cat frequently has direct contact. A somewhat curious clinical phenomenon is that patients often state that certain cats seem to be well tolerated and others bring on severe allergic symptoms. There is no evidence to suggest that certain breeds of cats or the length of the cat's hair correlates with the degree of allergen shedding from the animals. However, it has been shown that the degree of variability in the amount of *Fel d* I that is shed may be > 100-fold when comparing otherwise similar animals. It appears, on average, that male cats produce more *Fel d* I than female cats and that castration of male cats results in lower production of the allergen. This information may prove useful when allergic subjects insist on bringing a cat into the home.

Dog Allergy

Humans appear to have allergic responses to a variety of proteins that are present in the dander, saliva, urine, and serum derived from dogs. The main allergens appear to be

dog serum albumin and a protein named *Can f* I, but more than 20 possible allergens have been identified. There is some dog breed-specific variability in the production of these allergens, but all dogs have been shown to produce the main allergens. The large number of proteins that are potential allergens and the lack of well-standardized materials for diagnostic and research purposes have impaired adequate investigation of the effectiveness of environmental control for dogs. However, many of the environmental control methods that were discussed in the section on environmental control for cat allergy can be recommended for dog-allergic patients and can be modified as more elaborate investigations become available in this area.

Other Household Pets

The popularity of such pets as mice, rats, guinea pigs, hamsters, gerbils, and rabbits have made allergy to these animals an increasingly important clinical problem. One important finding is that the urine of rats, guinea pigs, mice, and rabbits contains substantial amounts of allergenic proteins that can be readily aerosolized and become airborne. This suggests that allergic patients should avoid contact with urine-contaminated bedding when the cages are cleaned. Routine environmental control measures for all household pets should include increased air exchange in the room where the pet is kept, confinement of the pet to a limited area of the home, minimal direct or indirect contact with the allergic patient and, ultimately, removal of the pet from the home if the patient's symptoms are severe or do not respond to other measures.

Cockroach Allergy

Cockroaches commonly infest the homes located in crowded cities of the United States and allergic sensitization to these insects is common in inner-city populations. Further studies are needed to define adequately the characteristics of the airborne antigens derived from these insects. Recommended environmental controls at this time include professional extermination, frequent "spot-cleaning" of cockroach-laden areas of the home, and efforts to minimize the availability of food sources for cockroaches. Unfortunately, factors that lead to rapid cockroach reinfestation are usually present in these environments, and meaningful environmental control of cockroach exposure in many domestic situations may be futile.

Indoor Mold Allergy

Fungi are organisms that are ubiquitous in our environment and may flourish indoors under the appropriate conditions. Several species seem to be the predominant indoor molds, including *Aspergillus*, *Penicillium*, and *Cladosporium*. In general, fungi grow in damp environments, such as basements (particularly in damp carpeting), window sills, crawl spaces, shower stalls, household dust, and in air humidification systems. Household plants can also be a substrate for mold growth.

These organisms can release a variety of potentially allergenic proteins and glycoproteins in the form of airborne spores, as well as secreted substances that may be aerosolized. Fungal allergens are not well characterized, although crude extracts of the organisms are potent allergens and can elicit vigorous immediate hypersensitivity responses during skin testing.

Environmental control measures for mold include avoidance of mold-contaminated areas and adjusting the climate to minimize mold growth. The most obvious measure is to have mold-sensitive patients spend as little time as possible in areas that are likely to result in considerable exposure (damp basements, crawl spaces, heavy house dust, bathtub/shower stalls).

Mold growth may be visible on carpet backing, in bathrooms, on concrete or cement block walls, or on damp wood surfaces. In these situations, the carpeting should be replaced, and other areas can be cleaned with bleach-based antifungal agents. However, a more appropriate long-term measure should be to decrease the indoor humidity by adjusting the home humidification system, or damp-proof the foundation to minimize indoor leaks and seepage. Most basements, particularly during the spring and summer months, are damp, and a portable dehumidifier can be helpful to remove water from the air and thus reduce the possibility of mold growth.

Mold will frequently contaminate both central humidification and freestanding humidification units that are present in many homes. These systems should be adjusted to avoid excess humidity in the home. The need for indoor humidification will change with climate, and many homes will not require routine use of a humidifier. If humidification is necessary, frequent cleaning of the unit is necessary to avoid contamination and dispersal of mold allergens into the air. Finally, such areas as bathrooms and kitchens should be equipped with appropriate exhaust mechanisms to evacuate steam, which may be episodically generated by cooking or running hot water.

"Outdoor Allergens"

Pollens and outdoor molds are common respiratory allergens, and avoidance when outdoors is difficult. However, pollen grains and mold spores are large enough that they cannot enter a home in significant amounts if the windows and doors remain closed. For this reason, at times of the year when outdoor allergens are abundant, the house should be closed, and if necessary, air-conditioning units can be used for temperature control. Air-conditioning also dehumidifies the air of the home, thereby reducing mite and mold growth.

ENVIRONMENTAL CONTROL OF IRRITANTS

A number of substances that can be detected in the air of many homes can be classified as irritants. The noxious effects of these substances are the result of their irritating effects on mucous membranes, such as those on the conjunctiva and respiratory tract. Sufficient exposure to these irritants results in ocular burning, itching, and redness, as well as symptoms of rhinitis and bronchospasm in susceptible patients. Irritant exposure will cause symptoms in all patients if the exposure is intense, but allergic and asthmatic individuals appear to have a low threshold of tolerance to these substances owing to chronic inflammation in the target organs of the nose, eyes, and lungs. The most common household irritants and recommendations for environmental control are listed in Table 4.

Tobacco Smoke

Tobacco smoke is a mixture of pollutants that include particulate substances and vapors that are capable of irritating human airways. Patients who are exposed to smoke

Table 4
Common Household Irritants and Environmental Control Recommendations

Irritants and their common sources	*Control recommendations*
Irritants present in environmental tobacco smoke Carbon dioxide Nicotine Benzene Formaldehyde Acrolein Particulate matter	Aid patient and family members in efforts to cease smoking "Necessary" or visitor smoking should be confined to outside the home (preferably) or in well-ventilated and exhaust fan-equipped areas Allergic patients should avoid cigarette smoke-laden areas of the home and other confined areas Area air cleaner equipped with an HEPA filter may be helpful for small areas like bedrooms
Examples of organic compounds Formaldehyde (building materials) Carbon tetrachloride (solvents) Toluene (paints, sealants) Aldehydes (perfuming agents)	Identification of the irritant source with adequate sealing of containers or removal from the home Increase ventilation in confined areas or throughout home when formaldehyde building materials are suspected Vapor-proof door seals between living areas and garage or work areas containing irritant substances Activated charcoal filter masks for intermittent unavoidable exposures Avoidance of perfuming agents, aerosols, and irritant cleaning solutions

have a high incidence of respiratory irritative symptoms, such as bronchitis and rhinitis, and there is a higher incidence of asthma attacks among children whose parents smoke. The only effective method to decrease environmental tobacco smoke is by encouraging smoking cessation and avoidance. Helpful "partial" controls include limiting smoking to outdoors, in well-ventilated areas, or areas of the home that are equipped with an efficient exhaust fan. However, in subjects with significant asthma, even minimal smoke exposure can result in exacerbation of their disease, and strict smoke avoidance is necessary.

Volatile Organic Compounds and Nitrogen Dioxide

This class of irritants includes diverse chemical substances that may be found in building materials, perfuming agents, personal care products, and household solvents. The primary sources of nitrogen dioxide include inadequately vented natural gas appliances and wood burning stoves and fireplaces.

Successful environmental control can only be accomplished with a high index of suspicion and knowledge of common sources for these irritants. Removal of the sources of volatile organic compounds and adequate venting of wood burning stoves and gas ranges can control levels of these important irritants.

Increasing fresh air exchange can be an effective method of decreasing any indoor irritant, since the sources of most of these compounds are inside the home and the concentration gradient favors improvement of the indoor environment with ventilation.

AIR-CLEANING DEVICES

Patients with allergies to indoor allergens typically ask whether it would be beneficial to purchase an air-cleaning device. Unfortunately, a clear answer to this question cannot be provided. A complex interplay of several factors is involved in determining the effectiveness of air cleaners on the levels of indoor allergens and irritants. These factors are discussed below.

Particle Size

Such allergens as pollens and dust mite are present on relatively large particles. These large particles become airborne with considerable disturbance, but rapidly settle back to the surface. Therefore, there is only a short period of time that the particles are subject to air cleaners (when they are airborne). This leads to a situation where large amounts of settled antigen cannot be filtered, and the small amount that is filtered will be replaced by newly produced antigen.

Mold allergens, the particulate components of environmental tobacco smoke, and a sizable fraction of the cat allergen *Fel d* I are present on small particles. Since these particles remain airborne for extended periods of time, they would be susceptible to air-cleaning devices capable of filtering small particles. However, at any given time, only a minute percentage of the total particles are airborne with an overwhelming amount remaining in large reservoirs, which serve to act as a "continuous source" of the airborne allergen.

Type of Air Cleaner

There are three basic classifications of air cleaners: mechanical filters, which clean the air by having the air pass through porous material where particles are trapped based on size; electrostatic precipitators, which impart an electrical charge on particles that subsequently adhere to surfaces of opposite electrical charge; and chemical filters, which rely on activated charcoal or other substances to absorb gases and odors.

The most beneficial mechanical filters include those that use an HEPA filter. These are capable of removing the vast majority of particles in the size range of the relevant allergens discussed above. The main problem, as discussed above, is that only airborne allergens will be filtered and only air from a limited area of the home will be drawn to the filter.

Electrostatic precipitators have been shown also to filter efficiently dust mite feces and pollen size particles (10–20 μ), and will remove a majority of the particulates generated from cigaret smoke. However, they require frequent cleaning and have the same limitations as discussed for the HEPA filters. The activated charcoal and chemical filters have variable effectiveness in their capability to absorb formaldehyde or nitrogen dioxide.

Several studies that were performed to investigate the effects of air cleaners on clinical symptoms have been inconclusive. Air cleaners are not routinely recommended to

patients for environmental control for indoor allergens or irritants. However, the use of air cleaners in conjunction with other environmental control measures has not been adequately studied. If patients have a strong desire to purchase an air-cleaning device, HEPA filter units appear to be the most capable of filtering the relevant allergen particle sizes and can be recommended for small area use.

APPROACH TO THE PATIENT

Patients with allergic rhinitis and asthma can benefit from sound advice pertaining to environmental control. However, advice needs to be tailored to each patient based on the severity of symptoms, the allergens involved, and the patient's personal circumstances.

History

A careful history is important in developing a sufficient index of suspicion for environmental allergen or irritant exposure. Careful inquiry in regard to the home and the workplace can yield information leading to a diagnosis of exposure to an occupational allergen or irritant. Questioning in regard to hobbies and outdoor activities may also provide clues to symptom-triggering exposures that may not be apparent to the patient. In many cases, the presence of an environmental allergy is obvious, such as "I sneeze, my eyes itch, and I wheeze whenever I hold my cat." However, chronic exposure to allergens or irritants more commonly results in the development of subacute or chronic symptoms, and the relationship to environmental exposure can often be missed.

Physical

Physical examination may be helpful in confirming the presence of rhinoconjunctivitis, asthma, bronchitis, or even urticaria, but these findings are unlikely to suggest a specific etiology.

Diagnosis and Recommendations

If the diagnosis is obvious and symptoms are mild, an empiric trial of appropriate environmental measures, with or without pharmacological treatment, may be indicated. When the history is unclear, or when symptoms are severe, evaluation by an allergist and relevant skin testing should be performed. Definitive recommendations for environmental control can then be made with confidence.

Recommendations for environmental control need to be tailored so that the patient is not overwhelmed or offended. For instance, most parents of children with mild rhinitis will not find it acceptable to pull up the carpeting, use acaricides, and take away their child's favorite stuffed toy for control of dust mite exposure. In fact, such extensive recommendations may lead to noncompliance with even the simpler measures of encasing the mattress, removing the feather pillow, and washing the bedding in hot water, which may provide significant relief of symptoms.

When symptoms are severe or progressing, such as is the case for a patient with progressive asthma, prompt confirmation of allergy and aggressive recommendations for environmental control are warranted. In many instances, it may be difficult to convince a patient that dust or animal contact is a problem. Many times, a positive allergy skin

test will provide a visible confirmation that may be helpful in persuading the patient that exposure to the allergen needs to be minimized.

In most instances, environmental control measures and pharmacotherapy will lead to a good clinical outcome for patients with rhinoconjunctivitis and asthma. It should be noted that many patients are sensitive to more than one allergen. Multiple allergies often result in symptoms that may not be clearly related to a single, obvious allergen exposure, and the effects of simultaneous exposure to multiple allergens may have additive effects on symptom severity. These subjects often need objective evaluation with skin testing or RAST testing (a method to detect specific IgE in the blood). In patients with refractory symptoms or extensive pharmacological requirements and known allergy, allergen desensitization therapy should be considered.

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23 Allergen Immunotherapy

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CONTENTS

INTRODUCTION

Allergen immunotherapy results in decreased sensitivity to allergens, observed clinically and demonstrated by laboratory techniques, in response to the gradual administration of increasing doses of allergenic extracts. Allergen immunotherapy is used to treat allergic rhinitis (hay fever), allergic asthma, and insect hypersensitivity. During the first half of the century, efficacy of allergen immunotherapy was based primarily on clinical observations. However, over the past 40 years, the fascinating, scientific investigations of allergens and of the immunologic complexities of the allergic reaction have improved our understanding of immunotherapy with allergens, such as pollens, molds, animal danders, house dust mites, and insect venoms. Allergen extract injections affect the immunologic response both systemically and at the mucosal membrane surface of the nose and bronchi. This chapter will address the subject of allergen immunotherapy for allergic rhinitis and/or allergic asthma. Immunotherapy for insect hypersensitivity is reviewed in Chapter 6.

HISTORY OF ALLERGEN IMMUNOTHERAPY

In 1903, an immunologic approach to the treatment of allergic diseases was initiated by Dunbar, who unsuccessfully attempted to immunize grass-sensitive hay fever subjects passively by applying antisera obtained from grass pollen-immunized horses and geese onto the allergic subject's nasal mucosa. Leonard Noon later suggested that active

From: *Allergic Diseases: Diagnosis and Treatment*
Edited by P. Lieberman and J. Anderson Humana Press Inc., Totowa, NJ

Table 1
Summary of Controlled Trials of Immunotherapy

						Danders	
	Grass	*Weed*	*Tree*	*Molds*	*Mites*	*Cat*	*Dog*
Allergic rhinitis	++	++	++	+	++	++	+
Asthma	+	++	+	+/–	+	++	+

– No effect.
+ Positive effect.
++ Strongly positive effect.

immunization with grass pollen vaccine should be attempted in subjects with allergic rhinitis who were allergic to grass. He had been working in Almroth Wright's laboratory, where prophylactic immunizations against typhoid fever had been successful, and his idea was a natural followup to that work. With the assistance of his sister, Dorothy Noon, who devised methods for collecting grass pollens, he began an active immunization program for grass-sensitive allergic rhinitis subjects.

Soon after Noon's preliminary, beneficial research work appeared in the literature, John Freeman published data indicating that subjects with allergic rhinitis were symptomatically improved after treatment with grass extract injections. Cooke, in 1915, formally introduced pollen immunotherapy into the United States by reporting the successful immunizations of 114 subjects with hay fever and/or asthma.

Injection therapy with allergens, first referred to as desensitization, was modified in many ways over the next 50 years and became an accepted method of treating allergic diseases (Table 1). Desensitization, however, now more appropriately refers to the temporary immunological tolerance induced by the rapid, repeated increasing doses of antigen as, for example, currently utilized to desensitize penicillin-allergic subjects who absolutely require the antibiotic. Hyposensitization refers to the decreased clinical sensitivity to allergens following allergen immunotherapy. Allergen immunotherapy is the most accepted term used today, because it is more descriptive of the form of therapy and the immunologic alterations that occur associated with the administration of allergen extract.

PRINCIPLES AND DEFINITION

Successful clinical improvement with allergen immunotherapy requires that first, the subject has symptoms of allergic rhinitis and/or allergic asthma after natural exposure to specific aeroallergens; second, the subject has skin test or serologic evidence of IgE antibodies to these aeroallergens; and third, the subject's symptoms improve once he or she has received a series of appropriately increasing doses of a specific allergen extract, preferably with defined potency (Table 2).

Sources of aeroallergens include, but are not limited to, pollens and molds, and animal emanations, such as dander, saliva, urine, and feces derived from such sources as

Table 2
Illustrative Dose Schedule for Short Ragweed Allergen Immunotherapy

Dose	*Vial*	*Dilution of 1:10 w/v concentration*[a]	*Dose, mL*
1			0.05
2			0.1
3	D	1:100,000	0.2
4			0.3
5			0.4
6			0.05
7			0.1
8	C	1:10,000	0.2
9			0.3
10			0.4
11			0.05
12			0.1
13	B	1:1000	0.2
14			0.3
15			0.4
16			0.05
17			0.1
18	A	1:100[b]	0.2
19			0.3
20			0.4

[a]1:10 Weight by volume (w/v) means 1 g of pollen is diluted in 10 mL of dilutent. Many allergists use w/v solutions for immunotherapy. 1:10 w/v Extract of ragweed contains 400 µg *Amb* a I (Ag E)/mL.
[b]The desirable dose is in the range of 3–12 µg.

When to Consider Allergen Immunotherapy

- Individuals with documented appropriate clinical symptoms, and either skin test or in vitro evidence of IgE-allergen-specific antibody.
- Allergic manifestations of rhinitis, bronchial asthma, or stinging insect venom sensitivity.
- Failure to respond to elimination or control of environmental allergic factors.
- Failure to respond to symptomatic medication or difficulty/inconvenience of using these medications regularly.

mammals, birds, insects, and house dust mites. A specific aeroallergen must be capable of inducing an IgE response, i.e., to be sufficiently abundant in the ambient air to sensitize and provoke symptoms in sensitized individuals.

Ragweed pollen hay fever is a model for aeroallergen-induced disease. First, ragweed pollen is a potent sensitizer in genetically susceptible or atopic individuals; second, the pollen is found in the air in sufficient quantities during the pollinating season to

sensitize many genetically susceptible individuals; and third, symptoms are induced in these susceptible individuals during and immediately following the ragweed pollinating season.

The immediate effects of allergen exposure are relatively easy to observe when they are caused by an allergen, such as ragweed, during the ragweed season or after cat or dog exposure. Such a temporal exacerbation of symptoms is evidence of a causal relationship; however, appropriately associating allergic symptoms and the natural exposure to a large number of different aeroallergens, for example, to various grass pollens and mold spores during the summer months is a more difficult clinical task. In such cases, the physician cannot always accurately determine the relative importance of each allergen to which the subject has a positive skin test. Therefore, it is incumbent on the physician to recognize which pollens, molds, and other aeroallergens are most prevalent in a geographic area and cause allergic symptoms. The American Academy of Allergy Asthma and Immunology has established a North American Pollen Network. This network has 78 certified stations. Information about regional allergens can be obtained by writing the American Academy of Allergy Asthma and Immunology (611 East Wells Street, Milwaukee, WI 53202).

More standardized allergen extracts with known potency are now available from extract manufacturers for skin testing and allergen immunotherapy. However, many of the allergen extracts currently utilized are not standardized and are not allergenically bioequivalent, even though they are similarly labeled. Ideally, an allergen extract should contain sufficient quantities of all of the allergens to which subjects become sensitized, a goal of the US Food and Drug Administration, which oversees the quality of extracts.

RATIONALE FOR IMMUNOTHERAPY

Some of the immunologic changes that occur with immunotherapy include:

1. A rise in serum IgG "blocking" antibody;
2. A blunting of the usual seasonal rise of IgE followed by a slow decline of IgE over the course of immunotherapy;
3. An elevation of IgG and IgA blocking antibodies in the respiratory mucosal secretions;
4. A reduction in basophil reactivity and sensitivity to specific allergens; and
5. Reduced lymphocyte responsiveness (proliferation and cytokine production) to specific allergens.

Favorable effects on symptom-medication scores and biologic or cellular hypersensitivity have usually been associated with a rise in serum levels of protective or blocking IgG and a decrease in the specific and total IgE (Fig. 1). The induced tolerance most likely relates to the changes that occur in lymphocyte populations, i.e., induction of TH_1 cells, which override the allergic promoting TH_2 cells. Not all immunologic changes associated with immunotherapy occur in all subjects, although there is general correlation between clinical improvement and altered immunologic parameters (Table 3). This reduction in biologic sensitivity to specific allergens has been demonstrated in allergen immunotherapy trials to such allergens as ragweed, mixed grasses, birch, and mountain cedar pollens, the molds *Alternaria* and *Cladosporium*, cat dander and house dust mites.

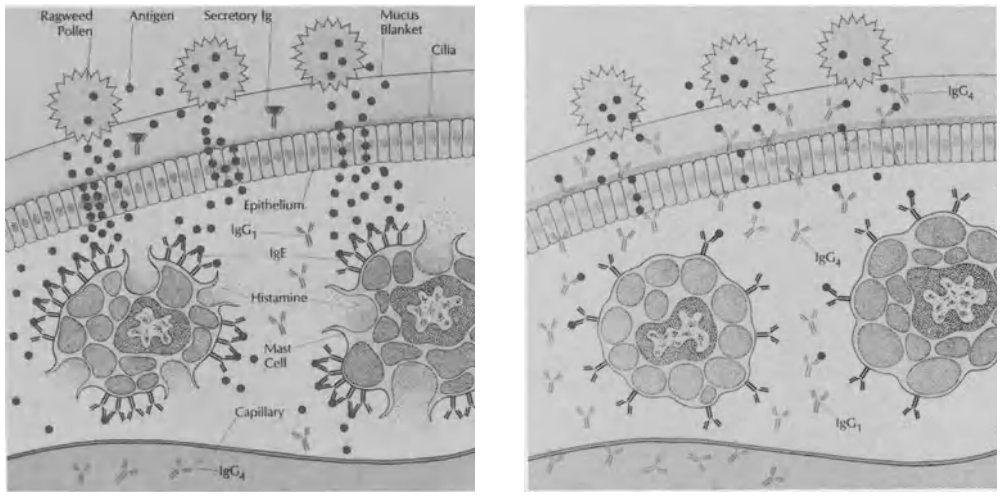

Fig. 1. Typically, serum IgG levels (and, to a lesser extent, secretory IgG and IgA) rise during immunotherapy, and the circulating immunoglobulin's subclass composition shifts from IgG_1 and IgG_4 to IgG_4 almost entirely. The therapeutic relevance of those changes is suggested in these diagrams. Without immunotherapy, exposure to an allergen (e.g., ragweed pollen) leads to uncontested crosslinking of antigen to mast cell-bound IgE **(left)**. With immunotherapy, such crosslinking may be prevented by increased secretory and serum immunoglobulins. In particular, IgG_4 would be well suited for this role because it is functionally monovalent and does not crosslink with antigen **(right)**.

Table 3
Proposed Immunologic Sequence of Events in Successful Immunotherapy

Step 1: Production of IgG blocking antibodies
IgG1 subclass antibodies early in the course
IgG4 subclass antibodies predominate later in the course
Induction of anti-idiotypic IgE antibodies (downregulation)
Step 2: Activation of antigen-specific suppressor T-cells (TH_1)
Downregulation of TH_2 lymphyocyte cytokine profile, which regulates IgE antibody production and eosinophil activation
Step 3: Reduction of target organ hypersensitivity and mast cell and basophil cellular sensitivity
Reduced cellular hypersensitivity
Reduced biological responses

Successful allergen immunotherapy ameliorates, but usually does not completely eliminate, the respiratory symptoms of allergic rhinitis and allergic asthma. When such therapy fails, reasons may include:

1. The inappropriate treatment of non-IgE-mediated disease, such as chronic nonallergic rhinitis or vasomotor rhinitis, with allergen immunotherapy;
2. Low allergen extract potency;
3. Insufficient doses of allergen administered;

4. Excessive environmental exposure, for example, to a cat or a dog, such that the allergen immunotherapy cannot ameliorate symptoms on exposure;
5. Coexistent medical problems, such as sinusitis or nasal polyps, which alone account for more of the symptoms than does the allergic rhinitis; and
6. Newly developed or previously undiagnosed sensitivities that have not been included in the allergen immunotherapy extract.

ADVERSE REACTIONS

Local Reactions

Patients receiving allergen immunotherapy often experience small local reactions (erythema and edema), which cause some discomfort at the injection site. No adjustments for reactions < 4 mm are usually necessary. Large local reactions, 4 cm or greater in diameter, occur less frequently, may cause more discomfort, and persist for 24 h or longer. There is a concern that subsequent increases in dose of the extract following a large local reaction may result in a systemic reaction. However, there is little evidence that such local reactions, whatever their size, definitely place the subject at increased risk for a systemic reaction. This local discomfort can be controlled with cold compresses and oral antihistamines. When such reactions occur, the subsequent allergen immunotherapy dose usually is reduced to the previously tolerated dose and subsequently increased. If large local reactions persist, the dose either has to be divided into two doses or not increased to higher doses.

Systemic Reactions

Systemic reactions occur rarely, and may be mild, manifested as generalized pruritus, urticaria, or symptoms of allergic rhinitis and conjunctivitis, to life-threatening, with upper and lower airway obstruction and/or anaphylactic shock. Fatalities are rare, but do occur. A retrospective survey by questionnaire of allergy specialists in the United States for the period 1945–1983 reported 46 fatalities either from skin testing or immunotherapy. The data of 30 of these allowed for further evaluation of the fatalities; six were caused by skin testing and 24 by immunotherapy. A later extension of this study included reports of an additional 17 deaths between 1985 and 1989 and 10 during 1991–1992. The estimated fatality rate from allergen immunotherapy in the United States was approx 1 per 2 million injections for the period of 1985–1989.

Precautions

Analysis of the allergic reactions and fatalities associated with allergen immunotherapy suggests that there are certain risk factors for a life-threatening systemic reaction or a fatality. Such risk factors include:

1. Unstable asthmatic subjects;
2. Patients experiencing significant seasonal exacerbation of their allergic symptoms, particularly asthma;
3. Patients who are highly allergic by skin or in vitro tests;
4. During the initial buildup period, particularly with accelerated schedules of immunotherapy;
5. High-dose maintenance regimens in highly sensitive allergic subjects; and
6. Concomitant use of β-blocker drugs for the treatment of hypertension, cardiac disorders, or migraine prophylaxis.

Local Reactions to Allergen Immunotherapy

- Redness and swelling (usually dime–quarter sized) are not uncommon and easily managed with an ice pack, with or without an antihistamine.
- Larger reactions may require aqueous adrenaline, 1:1000 (w/v), an antihistamine, as well as short-term oral corticosteroids.
- Significant local reactions require adjustment of subsequent allergen immunotherapy doses.

Risk of Systemic Reactions to Allergen Immunotherapy

- Risk rate: 1–2000 injections.
- Most reactions begin within 30 min of injection—thus, a minimum of 20–30 min waiting time is advised.
- More systemic reactions occur
  - In highly allergic patients.
  - With use of pollen-allergenic extract, during the pollen seasons.
  - During initial dose "buildup" phase, especially with accelerated programs.
- The risk of more serious reactions is increased:
  - In allergic asthmatics.
  - With patients on concomitant β-blocking drugs.

Therefore, no allergenic extract should be considered completely safe for an allergic subject, and immunotherapy should be carried out by trained personnel who know how to manage life-threatening adverse reactions in a setting where appropriate equipment for such management is immediately available. The risk of a fatal reaction should be reduced and, hopefully, eliminated by:

1. Careful selection of subjects who will benefit from such therapy;
2. Improved biological standardization of allergenic extracts; and
3. Better treatment of anaphylactic reactions, especially associated with severe asthma.

Additional precautions to decrease the likelihood of an anaphylactic reaction include decreasing the dose of extract during a seasonal exacerbation and withholding immunotherapy in a symptomatic asthmatic subject or in a subject whose peak flow or FEV_1 is <70% of his or her personal best or normal values. It also seems prudent not to institute allergen immunotherapy when subjects are on a β-blocker unless the benefit of allergen immunotherapy outweighs the risk of the subject being on a β-blocker. Some physicians have also suggested that all subjects or those at increased risk should be instructed in the use of and carry self-injectable epinephrine with them on the days of immunotherapy.

Requiring a 20-min wait by the subject in a medical facility following allergen immunotherapy injections is also advised. Longer waits are recommended for those considered at highest risk for a systemic reaction. A position statement on allergen immunotherapy of the American Academy of Allergy Asthma and Immunology allows for home administration of allergen immunotherapy injections, but only after the risk/bene-

Role of Allergen Immunotherapy in Asthma Management

- A consideration in asthmatics who are allergic: 80% of children over age 2 yr; 50% of adults
- A possible therapy in asthmatic, with concomitant significant allergic rhinitis—uncontrolled with environmental allergen elimination, plus rhinitis medication
- An adjuvant therapy in moderate–severe asthmatics who are not well managed with environmental allergen elimination plus asthma medication

fits are appropriately explained to the subject and documented, and when the subject has been appropriately instructed in the administration of his or her allergenic extract and epinephrine for the treatment of anaphylaxis.

CLINICAL TRIALS AND SCIENTIFIC STUDIES

Allergic Rhinitis

Many randomized controlled trials have shown the value of allergen immunotherapy for hay fever resulting from airborne pollens, animal allergens, and house dust mite aeroallergens. Efficacy for clinical improvement is based on subjective symptoms scores and medication diaries. Some studies demonstrate decreased basophil histamine release, reduced skin test sensitivity, and increased allergen-specific IgG blocking antibody following allergen immunotherapy (Fig. 2).

Nasal challenge studies have enabled investigators to measure the allergic response in the upper airway following allergen immunotherapy. Such research has demonstrated that there is a dose response to ragweed allergen immunotherapy. These data have been used to propose an optimal dose for inhalant immunotherapy. The first of these studies involved 12 ragweed-sensitive subjects who received immunotherapy, 6 μg AgE/injection (Antigen E [AgE] is the principal ragweed pollen allergen), for 3–5 yr compared to 26 untreated control subjects. Nasal provocation studies of treated subjects revealed that the AgE immunotherapy altered the clinical and the allergic inflammatory mediator responses (histamine, PGD2, TAME-esterase) to an intranasal ragweed challenge. In another later study, 27 previously nonimmunized, ragweed-sensitive subjects were randomized to three different dosage regimens (low to high doses; 0.6–25 μg AgE/injection) and their responses to ragweed nasal challenges compared. The low-dose immunotherapy regimen provided no protective effect, whereas the moderate-dose (12 μg AgE/injection) and high-dose (25 μg AgE/injection) significantly reduced mediator release from nasal secretions following nasal challenge. Symptom scores, recorded by the moderate- and high-dose treated subjects over three ragweed seasons, also improved significantly and correlated with the decreased release of inflammatory mediators following nasal challenge with ragweed allergen. There was no significant difference in the degree of clinical improvement between the 12- and 25-μg AgE groups. Other studies that examined the clinical efficacy of using the "optimal dose" of 6–12 μg AgE/injection consistently demonstrated clinical improvement. Therefore, the optimal dose of 6–12 μg of the major allergen for maintenance seems applicable not only to ragweed, but also to all other allergens, both inhalants and venoms.

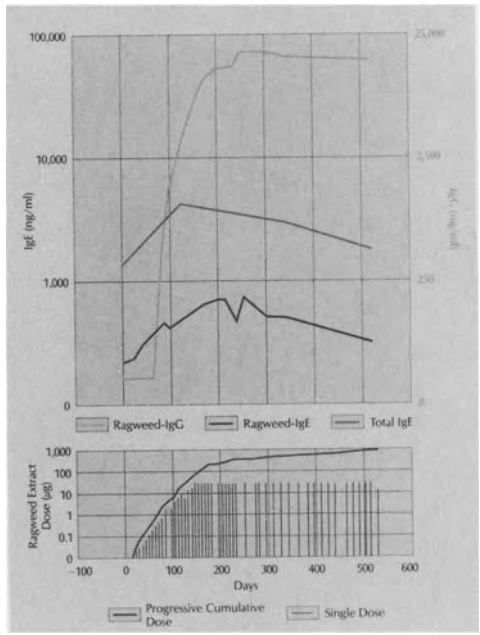

Fig. 2. When an allergic patient receives gradually increasing doses of the offending allergen, such as ragweed pollen extract, there is an initial rise in serum Ig levels, especially of allergen-specific IgG. Total and allergen-specific IgE levels may eventually decline, but IgG elevations persist. Typically, increased allergen-specific IgG correlates with favorable clinical response.

Nasal challenges also confirmed that such therapy attenuated both the immediate and late-phase allergic responses as evidenced by decreased mucosal membrane cellular influx and mediator production. Ragweed immunotherapy for 3–5 yr was required to achieve clinical remission.

Several mixed and single grass pollen immunotherapy studies for allergic rhinitis resulted in significantly decreased symptom-medication scores during the grass pollen season and responses to grass skin testing and nasal challenge testing. Increases in grass-specific IgG-blocking antibodies occurred in subjects successfully treated with mixed grass immunotherapy. The size of both the immediate and late-phase skin tests to timothy grass extract was diminished in a timothy allergen immunotherapy study, and the number of CD3 and CD4 T-lymphocytes in the late-phase skin test response was reduced.

Mountain cedar tree pollen extract immunotherapy decreased symptom-medication scores during the cedar tree pollen season, reduced the late-phase skin test reaction to mountain cedar pollen extract, increased the specific IgG, and decreased the seasonal rise in specific IgE during the mountain cedar pollination season. Similar studies have been done and results obtained with birch pollen allergen extract immunotherapy. In addition, birch pollen nasal provocation studies showed inhibition of allergic symptoms and reduced chemotactic activities for eosinophils and neutrophils in nasal secretions after allergen immunotherapy.

House dust mite allergen immunotherapy has significantly decreased nasal symptom scores, responses to nasal allergen challenge, and the size of the skin test reaction. The same changes in specific IgG and IgE as observed with pollen studies were found. *Alternaria* immunotherapy produced similar decreases in nasal symptom-medication scores, allergen provocative challenges in the skin and nose, and increased serum IgG. Cat allergen immunotherapy resulted in reduced nasal symptom scores of subjects exposed to a cat in a study room.

Allergic Asthma

More than 50 controlled immunotherapy trials have been performed with a variety of allergens for seasonal, perennial, and animal-induced asthma. Extracts of rye grass, mixed grasses, ragweed, birch, mountain cedar, *Alternaria*, *Cladosporium*, house dust mites, cat, dog, and cockroach have been used in these trials. Collective analysis of these studies provides important insights, but comparisons between studies are difficult because of varied study designs. Of these studies, 42 demonstrated significant clinical improvement in treated subjects. Twenty-three of these showed a significant increase in the bronchoprovocation threshold to the allergen extract used for immunotherapy. Of the trials in which immunologic parameters were monitored, 16 demonstrated an increase in allergen-specific IgG blocking antibody, and one showed a decline in specific IgE. Nine reported decreased skin test reactivity to the allergen used for immunotherapy, and two demonstrated reduced basophil histamine release following allergen challenge in vitro.

Allergic asthmatic subjects often have increased bronchial hyperreactivity during a specific pollen season. The effect of birch pollen allergen immunotherapy on bronchial reactivity, as measured by methacholine provocation, was investigated in subjects with birch pollen asthma induced during the birch pollen season. Untreated subjects had increased bronchial hyperreactivity to methacholine, whereas those on birch pollen immunotherapy did not. In addition, eosinophil cationic protein, an inflammatory mediator derived from eosinophils, in the bronchoalveolar lavage fluid was decreased in subjects receiving birch pollen immunotherapy.

The benefits of immunotherapy are specific for the allergen(s) used in treatment. Some studies have shown that single pollen allergen immunotherapy, such as derived from one grass species, may provide incomplete relief of asthmatic symptoms because of multiple grass sensitivity or because other sensitivities exist, for example, to molds. Similarly, highly purified standardized ragweed allergen extract containing only a single protein allergen, such as ragweed AgE, may provide incomplete relief of symptoms in ragweed-sensitive asthmatic subjects because they are sensitized to several ragweed allergenic proteins and not just AgE.

The IgE immune response of asthmatic subjects sensitive to several allergens is different from that of the monosensitized subject. Patients sensitized to a single allergen have significantly lower total serum IgE levels than those allergic to multiple allergens. The lymphocytes from the polysensitized subject, when challenged with allergen, express significantly more IL-4 and CD23 in vitro than does the monosensitized subject, although the interferon-γ production from lymphocytes is the same in both groups. These findings indicate that there is a difference in the IgE immune response and regulation of IgE between the polysensitized and monosensitized allergic subjects.

A double-blind placebo-controlled study during the pollen season compared the efficacy of immunotherapy in monosensitized and polysensitized asthmatic subjects. Subjects allergic to grass pollen extract were treated with an optimal maintenance dose of a standardized orchard grass pollen extract, whereas those allergic to multiple pollen species, including grass, received the same biologically equivalent dose of all standardized allergens to which they were sensitized. The results of this immunotherapy study indicated that subjects with orchard grass pollen allergy, but not polysensitized subjects, were significantly protected during the respective pollen season. Sustained and higher doses of standardized extract over a sustained treatment schedule may be needed to show efficacy in the polysensitized subjects. Subjects with asthma have more symptoms during the aggravating pollen season than during the out-of-season period. Therefore, less aggressive immunotherapy schedules are recommended.

Other controlled studies on the efficacy of immunotherapy in pollen-induced asthma have been completed. Some of these have demonstrated that asthmatic subjects receiving immunotherapy have a reduced late-phase allergic reaction following allergen provocation and reduced bronchial hyperresponsivesness to methacholine or histamine. These studies included the use of mixed grasses, cedar, birch, mugwort, and ragweed pollens. A 5-yr study of the role of immunotherapy in ragweed-induced asthma was conducted at Johns Hopkins University and reported in 1993. Clinical parameters (symptom diary scores, medication usage, PEFR measurements, and physician evaluations) and other end points (skin test sensitivity, serologic parameters, and bronchial sensitivity to ragweed and methacholine) were monitored. A standardized, maintenance dose of ragweed extract containing *Amb a* 1, 10 μg/injection, was used to immunize ragweed-sensitive subjects. Both clinical and objective parameters improved again, demonstrating that the use of an appropriate therapeutic dose is necessary to achieve a good clinical response.

Various studies of immunotherapy with extracts of standardized aqueous *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae* demonstrated significant benefit. Bousquet's study revealed that among subjects allergic only to *D. farinae*, children showed a significantly greater improvement than did adults. Patients with severe, chronic asthma ($FEV_1 \leq 70\%$ of predicted), with other perennial allergy sensitivities, with aspirin intolerance, or with chronic sinusitis achieved the least or no benefit from immunotherapy.

A later study by Bousquet et al. analyzed immunotherapy to *D. pteronyssinus* in 74 mite-allergic asthmatics. It demonstrated a significant dose-dependent increased tolerance to the standardized *D. pteronyssinus* allergen, *Der p* I, on bronchial allergen challenge in each of the immunized groups with no change in the control group. A significant reduction in histamine bronchoprovocation hyperresponsiveness also was observed with the greatest reduction in the highest-dose group. The rate of systemic reactions was lowest in the low-dose and highest in the high-dose group, and since the 7 and 21 μg/injection schedules were equally effective, the 7 μg/injection dose was recommended as the appropriate target dose. Bousquet's studies indicate that more immunotherapy-related asthmatic reactions occurred in mite-allergic asthmatic subjects than among pollen-allergic asthmatic subjects. Systemic reactions occurred less often during maintenance therapy than during the buildup period, and exclusion of subjects with severe or unstable asthma reduced the rate of significant systemic reactions.

Several controlled studies found that immunotherapy effectively increases the threshold dose of cat or dog dander extract needed to induce a positive bronchial challenge in subjects with cat- or dog-specific allergic asthma. Such therapy also resulted in a reduction of symptoms after dander exposure in a challenge room. Many subjects are given cat or dog immunotherapy, at their own request, in an effort to tolerate better the presence of a pet in their home. However, confirmation of clinical efficacy under such circumstances is needed, and elimination of the animal from the environment in which the subject lives is the preferable mode of therapy.

Molds that trigger asthma are numerous, diverse, and contain multiple allergens, and most mold extracts available for use in the United States are not standardized. Controlled immunotherapy trials with standardized extracts of *Alternaria* and *Cladosporium* were effective in the treatment of asthma. One such trial with 1-yr treatment with *Alternaria* resulted in ablation or a reduced late-phase response on *Alternaria* allergen challenge in 8 of 10 subjects. Increased concentrations of allergen and methacholine also were required to induce bronchial constriction. *Cladosporium herbarum* extract immunotherapy produced significant decreases in symptom-medication scores and response to bronchial challenge tests. Many of the same in vitro changes were observed in this study. A meta-analysis of randomized, controlled trials of allergen immunotherapy in asthma published in 1995 supports the view that allergen immunotherapy is effective to treat allergic asthma, provided that a clinically relevant and unavoidable allergen can be identified.

CURRENT AND FUTURE TRENDS IN IMMUNOTHERAPY

Chemically modified allergens have been tested in allergic subjects. Results demonstrate that glutaraldehyde or polyethylene glycol-modified allergen extracts are effective, and that fewer injections are necessary with such extracts than with aqueous extracts. Chemically modified allergens for immunotherapy have not been licensed by the FDA in the United States.

Recombinant allergens produced from genes cloned into an expression system, such as *Escherichia coli*, or a yeast have been produced to diagnose and treat allergic diseases. Studies with these specific, well-defined characterized proteins provide more precise immunologic information about immunotherapy. However, these recombinant proteins are not necessarily equivalent to native allergenic proteins because of possible differences in the three-dimensional structures and configurations of the molecules. A variation from the native protein may result in less specific immunologic recognition.

Once a protein is cloned and synthesized, it seems possible to design a peptide molecule that does not interact with IgE, but still engages the specific T-cell receptor. Peptide binding of the T-cell receptor will theoretically inhibit the activation of the T-cell and, in particular, the TH_2 cell that is central for IgE production.

Given the extensive evidence that T-cells play an important role in allergic disease, it seems logical to develop novel targets of immunotherapy, whereby the allergen peptide directly interferes with T-cell activity. These molecules theoretically should not precipitate an allergic systemic reaction, thus eliminating the current risks inherent with today's form of allergen immunotherapy.

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24 Controversies in Allergy and Allergy-Like Diseases

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CONTENTS

INTRODUCTION

The management of allergic diseases is accomplished most successfully and cost effectively by the patient's primary care physician in collaboration with a specialist in allergy/immunology. It is critically important to use methods of diagnosis and treatment that are based on sound scientific principles and that have been validated by proper clinical trials. Physicians who treat allergic patients, therefore, must be aware of the plethora of unproven and controversial methods that are currently promoted by a small group of practitioners, and they should understand the faulty rationale on which they are based. These unproven techniques and their unscientific, or even antiscientific theories are sometimes deceptively labeled as alternative or complementary forms of medical practice. This implies some measure of efficacy that in fact does not exist.

In contrast to the extensive immunopathologic foundation of basic and clinical research underlying our present knowledge of human allergy, the theories advanced by the proponents of the controversial methods described in this chapter lack experimental proof. These theories frequently arise from misinterpretations of chance empiric observations.

UNCONVENTIONAL THEORIES OF ALLERGY

The principal theories on which most of the unproven allergy practices are based are listed in Table 1. The theory of allergic toxemia is a generic concept that underlies several of the currently held unproven ideas about the etiology and scope of allergic dis-

From: *Allergic Diseases: Diagnosis and Treatment*
Edited by P. Lieberman and J. Anderson Humana Press Inc., Totowa, NJ

Table 1
Unproven Allergy Theories

Allergic toxemia
Environmental illness
Food additive sensitivity
Multiple food allergies
Multiple chemical sensitivities
Candida hypersensitivity

eases. It is comprised of two mistaken components. First, it assumes that allergens are inherently toxic, and secondly, that virtually any subjective symptom in the absence of objective evidence of pathology can be attributed to allergy. In fact, most allergens are intrinsically nontoxic in the usual dosage and manner of exposure necessary either to induce or elicit an allergic reaction. The presence or absence of potential toxic properties of an allergen is irrelevant to its ability to evoke an allergic immune response. Furthermore, the manifestations of allergic illness result from inflammation, and are therefore expressed in both symptoms and objective physical signs of the allergic inflammatory response. In contrast, most proponents of allergic toxemia in its various forms diagnose the condition in patients with multiple vague symptoms that usually include fatigue, anxiety, cognitive difficulties with memory and concentration, and a variety of physically unexplained pains and other bodily discomforts.

The allergic toxemia concept originated with patients who attributed their multiple medically unexplained symptoms to their diet. This led (or misled) to the theory that multiple food allergies in a single individual can produce an unlimited number of symptoms, and that the specific symptoms and implicated foods are variable and changeable. Other ingested substances, such as food additives and prescribed medications, particularly antibiotics, are frequently implicated as causes of allergic toxemia. In order to explain unpredictable symptom responses, the concepts of "masking" and "overload" were devised to rationalize the absence or presence, respectively, of unexpected symptoms. The current terminology for unexplained absence/presence of symptoms is "adaptation/deadaptation." It is clear that these terms are merely descriptive and have yet to be explained by their advocates in a physiologically meaningful way.

Environmental illness and multiple chemical sensitivities are names applied to a condition described above as allergic toxemia, but in this case, the cause is attributed to numerous common everyday environmental chemicals. In most cases, these chemicals include pesticides, solvents, perfumes, new carpets, plastic materials, new clothing, and virtually any synthetic chemical or commercial product with an odor. Occasionally, electromagnetic fields generated by nearby electric power lines or even household appliances are included as causes of symptoms. Some patients believe that their multisystemic polysymptomatic illness represents a hypersensitivity to numerous chemicals, foods, and drugs. The term given to this condition is "universal allergy."

Periodically over the past century, this clinical condition has also been ascribed to the effects of a specific microorganism, usually one that enjoys a normal, symbiotic or commensal relationship with the human organism. Formerly called "autointoxication"

Unconventional Theories

The concept of allergic toxemia, environmentally derived illnesses, or sensitivities owing to long-term (low-dose), multiple chemical exposure, which can result in immune "dysfunction," was first proposed 40–50 yr ago. These theories remain unproven today and are unacceptable to the majority of the medical community in the United States.

when it was believed to represent the toxic effect of the normal gastrointestinal microbial flora, more recently this concept has reappeared as a presumptive chronic viral disease. In this case, according to one unproven theory, the persistence of a virus, such as the Epstein-Barr Virus or the human herpesvirus 6 (HHV-6), was postulated to cause chronic "activation" of the immune system. There is no substantiated evidence or even a clear definition of what "activation" means in this context, and there is no proof currently that persistence of any virus can explain the pattern of symptomatology experienced by such patients. A variant of this theory is the so-called *Candida* hypersensitivity syndrome, attributed to the existence of Candida albicans on certain mucous membranes of many healthy individuals.

CONTROVERSIAL METHODS OF ALLERGY DIAGNOSIS

In order to select the most appropriate methods for diagnosis and treatment, the clinician should be familiar with the underlying principles and the procedures involved in both legitimate and unproven methods that are currently available. The controversial methods purported to be useful in diagnosis and those recommended for treatment will be discussed separately (Tables 2 and 3). Some of these procedures are of no proven worth under any circumstance, whereas others may have a legitimate place in some conditions, although not in allergic disease.

The provocation-neutralization procedure consists of "testing" the patient with a small amount of a substance in liquid form administered by either intradermal injection or by sublingual drop. The patient records any symptoms or sensations for a period of 10 min thereafter, and any symptom, regardless of its nature or intensity, is taken as an indication that the test is "positive." If the patient fails to report a symptom, the test is repeated using the same test substance at a different concentration until there is a "positive" result by these criteria. Next, the same substance is tested at lower concentrations until the patient again fails to report a symptom, at which point the allergy (i.e., the symptom) is said to be "neutralized." The neutralizing dose of the substance is then prescribed as a form of treatment.

Substances used in this procedure are numerous and include the common atopic allergens, food extracts, chemicals, drugs, and hormones. Because each test substance must be administered separately to elicit symptoms, testing to multiple substances is extremely time-consuming. It has been shown, however, that patients cannot distinguish test extracts from placebo controls by this procedure, so the basis of a positive test is merely the power of suggestion. This procedure is therefore worthless for diagnosis, and there is the potential danger that delivery by the sublingual route of an allergen to a

Table 2
Unconventional Diagnostic Methods

Provocation-neutralization
Cytotoxic test
Pulse test
Applied kinesiology
Electrodermal testing

Table 3
Unconventional Treatment Methods

Neutralization
Food avoidance
Chemical avoidance
Vitamins and other supplements
Enzyme-potentiated desensitization
Acupuncture
Homeopathy

patient with a true IgE-mediated allergy might cause life-threatening angioedema of the buccal mucosa or even systemic anaphylaxis.

The cytotoxic test consists of applying a drop of the patient's blood onto a microscope slide containing a minute quantity of a food or drug. The unstained blood sample is then inspected microscopically for alterations in the morphology of the leukocytes, which is said to indicate allergy to the food or drug. There is no standardization of this procedure regarding the percent of abnormal leukocytes that constitutes a positive result, time of incubation, pH, temperature, or any other variable that might affect leukocyte viability. There is no reasonable theory linking changes in blood leukocyte appearance and allergic disease. There have been no studies to correlate the result of this test with a rigorous independent proof of allergy, such as the double-blind, placebo-controlled oral food challenge.

The pulse test for food allergy is performed by measuring the pulse rate of the patient before and after food ingestion. Remarkably, advocates of this "test" have claimed at various times that an increase, a decrease, or both are diagnostic of food allergy. There is no independent verification that a pulse change correlates with allergy, nor is there a cogent theory to explain such a phenomenon. The pulse test is an example of a valid medical diagnostic procedure—quantitation of the pulse rate—being misused as an allergy test.

Applied kinesiology is a purported system of health practice that is based on the bizarre concept that a variety of diseases, especially allergy, cause a reduction in the strength of skeletal muscle. The diagnosis of food allergy consists of subjectively testing the ability to resist the forced movement of the patient's outstretched arm during exposure of the patient to a food. Incredibly, the exposure to the presumed food allergen is usually done by placing the food in a container, which the patient simply holds during

Methods that Could Be Considered Experimental

- Diagnostic procedures
  - Intradermal or sublingual drop provocation/neutralization
  - "Vega" electrodermal testing
- Treatment procedures
  - Sublingual or injection (low-dose) immunotherapy
  - Enzyme-potentiated desensitization

the muscle strength testing. Not surprisingly, there is no experimental proof of either the diagnostic efficacy of the procedure or validation of its theory.

The suggestive power of a mechanical or electrical apparatus in medical diagnosis is illustrated by electrodermal diagnosis. In this case, a device to measure the electrical resistance of the skin is inserted into a circuit that includes a metal container of a food item and a probe applied to the patient's skin. The probe presumably explores various points on the body surface, and a change in the galvanic resistance of the skin is believed to indicate allergy to the food being "tested."

CONTROVERSIAL TREATMENTS FOR ALLERGY

Treatment regimens that are based on unsubstantiated theories of allergy or unreliable diagnostic tests are clearly not in the patient's best interest. Those discussed here are listed in Table 3. The fact that a patient might seemingly benefit from a particular form of treatment, especially if the illness is largely or completely subjective, does not validate the treatment. Clinical efficacy and safety can be evaluated only by a properly designed and executed controlled trial with appropriate measurements and analysis. The controversial forms of allergy "treatment" described here have either failed critical tests of efficacy and safety, or they have not been evaluated because of the lack of any compelling reason to do so.

Neutralization therapy is an extension of the provocation-neutralization testing procedure described earlier in this chapter. The so-called neutralizing dose of the test substance is prescribed for self-administration by the patient either to relieve current symptoms or to prevent symptoms when they are believed to be imminent because of an anticipated environmental exposure. The treatment is also recommended on a regular schedule as an ongoing maintenance program. The neutralizing solution is taken by either sublingual drops or by subcutaneous injections. There is no evidence of any therapeutic result other than a placebo response.

Avoidance therapy is as frequently recommended as a feature of most controversial forms of allergy practice as it is in conventional practice. The differences, however, are profound with respect to the underlying rationale and the extent and consequences of the recommended program.

The various unreliable diagnostic tests that have been described here invariably "uncover" an extensive list of nonexistent allergies, leading to the unnecessary elimination of numerous foods and the avoidance of environmental items that are ubiquitous in

today's world. Extreme elimination diets are obviously dangerous, so proponents of the concept of multiple food allergies usually advise their patients to eat (or to avoid eating) specific foods on a prescribed schedule, usually as a 4- or 5-d rotational diet. Proponents of the rotational diet also claim—without substantiation—that such a diet actually prevents the development of food sensitivities. Chemical avoidance for patients with so-called multiple chemical sensitivities may be so extreme that major lifestyle changes are necessary to avoid any possible exposure to all synthetic products and all items that can be detected by odor. Fortunately, most of those individuals who have been diagnosed with multiple food and chemical sensitivities eventually compromise on these extreme recommendations.

Dietary supplements are frequently a component of these irrational approaches to allergy management. Although there is neither theoretical nor experimental evidence that allergy pathogenesis involves a deficiency of any nutrient, clinicians and others who promote any of these "alternative" programs usually advise their patients to take supplemental vitamins, minerals, amino acids, chemical antioxidants, or some combination of these.

A number of unmedical, unscientific, and unproven systems of practice offer to help persons with a variety of illnesses, including allergy. The most prevalent today are acupuncture, chiropractic , homeopathy, and naturopathy, but there is also a long list of boutique "therapies," such as crystal therapy and herbalism. In general, each of these treatment-based systems employ a similar or even identical treatment procedure, regardless of the nature of the disease. Needless to say, needling of the skin, spinal manipulation, ingestion of herbs, or any of the other maneuvers embraced by these entities are inconsistent with the known mechanisms of allergy, and proponents of them cannot cite any evidence of effectiveness.

Many of the unconventional treatments discussed above are recommended for patients with presumed allergy in whom the existence of a true hypersensitivity disease is questionable. Recently, an unproven "modification" of allergen immunotherapy for patients with atopic allergy has surfaced. It is called enzyme-potentiated desensitization, and it consists of a single preseasonal subcutaneous injection of a conventional pollen extract mixed with a minute quantity of the enzyme β-glucuronidase. It is claimed to be superior to the usual extended course of immunotherapy, which requires graduated increasing doses of allergen leading to a successful long-term maintenance program. Although a single low-dose injection of an allergen is certainly less likely than conventional immunotherapy to cause a systemic reaction, there is no evidence that enzyme-potentiated desensitization favorably affects atopic disease, whereas there are now dozens of well-controlled clinical trials confirming efficacy of the conventional high-dose form of treatment.

DISCUSSION

The superficial similarity of many of these unproven methods to scientifically based procedures of diagnosis and treatment of allergic diseases is an opportunity for exploitation by their proponents and a trap for the unwary clinician. The allergic population is very large, and the primary care physician is the first medical contact for most of them. Practitioners of unconventional procedures are readily available both within and out-

side the medical profession. They often advertise their services with promises that most physicians cannot and do not make. Only by knowing the specifics of these methods and their claimed theoretic basis can the clinician make an informed decision and give proper advice to the patient about their use.

With the exception of sublingual allergen administration, the methods reviewed in this chapter are not likely to pose an immediate hazard to health. Rather, their danger is more subtle, pervasive, and profound. An incorrect diagnosis made by an unreliable test creates the risk that another disease—physical or psychiatric—remains undiagnosed and untreated. Diagnosing allergy in a person who truly has none may create a lifelong disability characterized by unnecessary avoidant behavior. An extreme form of this unfortunate iatrogenic phenomenon is seen in patients who accept the idea that they have multiple sensitivities to foods and/or chemicals. Some of these individuals live a life of social and material isolation from which they will likely never recover. Most allergists would agree that it is far easier to treat an allergy than it is to disabuse a patient of his or her fear of an allergy that does not exist.

The problem of unconventional methods in allergy is of concern to a number of professional societies. In particular, the American Academy of Allergy Asthma and Immunology has published position statements about many of these procedures. These publications also provide literature citations to appropriate studies and evaluations that document their lack of effectiveness.

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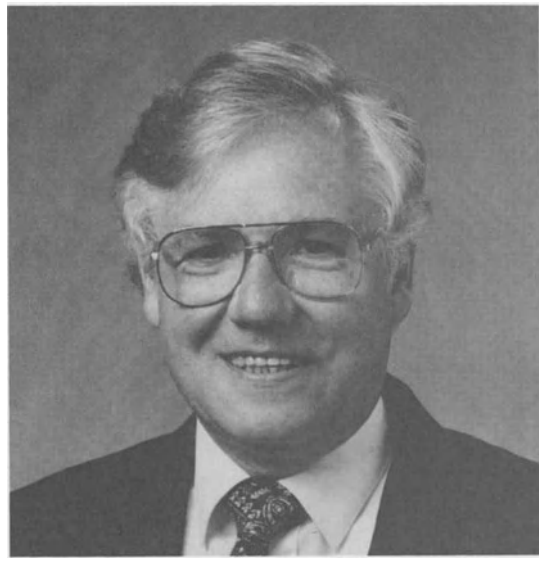

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