Chapter 44: Allergic Rhinitis

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Allergic rhinitis can be defined as congestion of the nasal mucous membrane accompanied by rhinorrhea and sneezing. Two elements required for its development are an immunologic sensitivity to an allergen and a recurrent or continuous exposure to it. This disease is triggered by a variety of allergens and mediated by specific IgE antibody. It is therefore a distinct clinical entity distinguishable from other forms of rhinitis by the following traits:

1. Usually early onset (age 1 to 20 years).

2. Strong family tendency.

3. Propensity for clustering with other allergic disorders (for example, eczema, asthma, and conjunctivitis).

4. Often elevated serum levels of total IgE antibody (usually greater than 100 units/mL).

5. Tendency for elevated specific IgE levels demonstrable by positive results of skin tests, nasal challenges, and in vitro procedures (for example, radioallergosorbent test (RAST)).

6. End organ hypersensitivity to a variety of chemical mediators of inflammation (for example, mecholyl)).

7. Increased lower airway reactivity.

Although allergic rhinitis is usually a mild disease, it can make patients extremely uncomfortable and interfere with sleeping, eating, and life-styles. In addition, afflicted individuals often develop secondary sinus infections, serous otitis media, and nasal polyps. They even have four times the risk of developing asthma as do individuals without such allergies (Settipane, 1983).

Historical Perspective

In the nineteenth century, at the time the condition was first described, hay was incorrectly believed to cause the disorder, and the term *fever* was loosely applied to many conditions (Bostock, 1819). Unfortunately, the misnomer *hay fever* is still in wide use. As early as 1829 Gordon pointed out that the term was misdirected and observed that patients "could pass through the most luxuriant meadow with impunity as soon as the flowers had died away, although they had suffered increasingly as the flowers approached perfection". He still was off the mark, however, because he attributed the trouble to the scent of the grass flowers. In 1830 Elliotson rejected these theories and was the first to identify pollen as the problem source when one of his patients reported that his symptoms peaked when the grass

came into flower and subsided when he stayed indoors.

Over 40 years later Blackley (1873) suggested that pollen be used to test for sensitivity. He found that when pollen samples collected during the flowering season were sniffed 6 months later - in the middle of winter - they produced typical nasal symptoms. By exposing glass plates moistened with glycerin outdoors, he succeeded in demonstrating that the air is heavily charged with pollen during the hay fever season. He also mounted similar glass plates on kites and sent them to heights of 500 meters and recorded that they also became coated with pollen. This latter finding led him to conclude that windborne pollen could cause distress, even at great distances from the original source. He also observed that rubbing pollen into a scratch on the arm elicited a strong adverse reaction in the skin. This reaction was, to him, the final evidence of the true cause of allergic rhinitis.

Today we recognize that environmental agents other than pollen can start the allergic response in susceptible individuals. These triggering substances range from mold spores, house dust constituents, and animal danders to foods, debris from insects, and even the aromas from various chemicals. Most antigens are 2 to 50 microm in diameter, and their allergenic constituents are usually proteins with a molecular weight between 10.000 and 40.000 daltons.

Incidence

Estimates suggest that 17% of all Americans have at least one form of allergic disease; 15 million patients have allergic rhinitis alone. In a survey of college students, Hagy and Settipane (1969) found that 26% experienced allergic rhinitis. Even this figure is deceptively low, however, since it does not include the many individuals who could have had the condition in the past but have since recovered.

Allergic rhinitis can start at any age; it has been detected in infants as young as 6 months of age and newly diagnosed in the elderly. Typically, it starts before the age of 40, and usually onset is between the ages of 12 and 15 years. Viner and Jackman reported in 1976 that over 30% of 1271 patients diagnosed as having perennial rhinitis reported that their symptoms first appeared before they were 10 years old.

Genetic factors

Patients who have a strong family history of allergies seem to have a special predilection for becoming immunologically sensitive to common environmental allergens. In the first comprehensive study of the role of heredity in atopy, Cooke and VanderVeer (1916) found that 48% of allergic patients had an immediate family history of allergies, whereas only 12% of a nonallergic group had such a history. Among individuals with a bilateral family history of allergy, 68% developed symptoms before age 10. In another study 85% of patients with a positive family history of allergy had the onset before the age of 20 (Smith, 1974). Hamburger et al (1974) found that when both parents were atopic the risk of children developing atopic disease was 47%, whereas when only one parent was atopic the risk was 29%. Current data indicate that the mother's history of severe allergy is more significant than

the father's in predicting atopy in an offspring.

Although the disease of allergic rhinitis is clearly familial, the details of genetic control are yet to be determined. Association studies, in groups of unrelated allergic individuals, provide support for the theory of influence of HLA-linked Ir genes in the expression of allergy (Cohen, 1974; De Weck and Blumenthal, 1977). These studies demonstrate correlations between specific HLA antigens and skin test responsiveness to grass and ragweed components.

Several investigators have noted that early elevation of serum immunoglobulin E (IgE) levels may presage the development of allergic disease. Kjellman (1976) reported that cord serum IgE levels correlated significantly with the subsequent development of atopic disease. Michel et al (1980) reported that only 21% of symptom-free infants had detectable serum IgE in the cord blood at birth, as compared with 71% of infants who subsequently developed clinical disease.

Soothill et al (1976) noted a significantly greater proportion of abnormally low levels of serum immunoglobulin A in atopic subjects. His conjecture is that atopic disease is a result of overstimulation of the IgE-forming cells in children at a time when their serum IgA levels are still low. Taylor et al (1973) have suggested withholding commonly allergenic foods from the diets of these children until their intestinal tracts become coated with their own IgA immunoglobulin. Others, however, have found IgA levels to be higher in atopic children than in nonatopic ones. Gerrard (1984) has reported similar findings in adults.

Environmental factors

Observations made in 1931 by Coca and Grove on patients living among pollens of limited geographic distribution give evidence that a primary exposure to a specific pollen was required to evoke an allergic disease. Rhinitis patients living in Europe were tested with extracts of pollen from ragweed (which does not grow on that continent), and only 1 of 36 individuals tested reacted. The sole person who reacted positively was known to have traveled to the USA and to have been exposed to ragweed pollen. Similar studies performed on populations with extraordinary exposure to sugar beet pollen and castor bean dust showed a considerably higher rate of allergic symptoms and positive skin reactions to these allergens than was found among atopic patients without comparable exposures (Seebohm, 1978).

The season of birth seems to be another factor predisposing individuals to allergic rhinitis. Settipane and Hagy (1979) found that those born in the months of May through September show the highest vulnerability to ragweed pollinosis. Bjorksten et al (1980) found that Scandinavian patients born between February and April have a greater risk of developing birch pollen allergy than do their countrymen born at other times of the year. Another recent study has reported an increased incidence of house dust mite allergy in patients born in the months of May through September, when mites are most abundant (Korsgaard and Dahl, 1983).

Physiology

Although the precise offending allergen may be difficult to discover, allergic rhinitis by definition is a disease of known pathogenesis. On exposure to inhaled allergens, genetically predisposed atopic individuals have high and prolonged IgE antibody responses within the lymphoid tissue of the respiratory tract. This antibody becomes fixed via its Fc region to specific receptor sites on the surface of blood basophils and tissue mast cells (Ishizaka and Ishizaka, 1971; Wasserman, 1983). Perturbation of the mast cell membrane receptor by IgE cross-linkage secondary to antigen binding is followed by a series of biochemical reactions that lead to the subsequent degranulation of the cell and the release of potent chemical mediators such as histamine, the slow-reacting substance of anaphylaxis (SRS-A), eosinophilic chemotactic factor (ECF-A), and others (Table 44-1).

Table 44-1. Mast cell mediators*

Preformed	**Newly synthesized**
Histamine	Leukotrienes (SRS-A)
Serotonine	Platelet-aggregating factor (PAF)
Eosinophilic chemotactic factor of anaphylaxis (ECF-A)	Prostaglandins
Neutrophil chemotactic factor	Kallikrein-kinins
Chymase	Lipid chemotactic factor
Heparin	
Arylsulfatase A.	

* These compounds are the major pharmacologically active mediators released following perturbation of the mast cell from either atopic or non-atopic mechanisms.

These pharmacologically active molecules released within the nose cause variable degrees of vasodilatation and edema (nasal congestion), an increase in mucous secretion and cellular recruitment (rhinorrhea), and increased capillary and mucosal permeability, permitting allergen contact with additional mast cells lying within the submucosa and thereby magnifying the reaction. The allergic reaction also disturbs the autonomic nervous system's finely balanced control of nasal function. As the rhinitis progresses, the response to allergic stimuli becomes exaggerated.

Connell (1968) has described a "priming" response in which a larger dose of allergen is needed to produce the same response on previously unchallenged mucosa than is required after a week of daily exposure. He lists four characteristics:

1. The response begins within 24 hours after the first allergen challenge.
2. Reversal commences approximately 48 hours after the last challenge.
3. The response is a local phenomenon.
4. The response is nonspecific; that is, a nasal membrane primed by one antigen is primed to all other antigens to which the patient is allergic.

Physical stimuli, irritants, and emotional factors may also cause nonspecific enhancement of nasal symptoms. The threshold is lowered to a point at which even a change in temperature or the presence of noxious fumes can cause sneezing paroxysms and watery rhinorrhea.

Pathology

Histologic findings in allergic rhinitis patients consist of mucosal edema and colloidal disaggregation of the tunica propria with an infiltration of eosinophils, lymphocytes, and plasma cells. The tunica propria, which lies beneath the basement membrane and has been postulated to be a barrier to penetration of foreign material, appears to be thin or destroyed in some patients having symptoms for a considerable period of time.

Numerous studies have been designed to determine whether patients with atopic rhinitis have a defect in the basement membrane that permits inhaled allergen macromolecules easier access to both the antibody-producing cells and the sensitized tissue mast cells in the perivascular sites within the submucosa. In 1964 Salvaggio et al found that atopic subjects have increased permeability to antigens instilled in the nose, and in 1975 Buckle and Cohn made similar observations. In his 1970 research study Connell biopsied nasal membranes before and after allergen challenge and noted marked changes both in the number and type of cells found in the tunica propria and in the basement membrane. On the side of the nose primed with ragweed pollen, the membrane was fragmented and had only a fraction of the thickness of the normal membrane. Okuda, however, presented data in 1982 suggesting that basophilic cells on the mucosal surface play a more important role in nasal allergic reactions than do mast cells in the lamina propria. He studied the final distribution of both dried and radiolabeled soluble ragweed pollen placed on localized areas of the inferior turbinate in patients with ragweed pollinosis. Using biopsy specimens taken after the onset of symptoms, Okuda found that most of the material was localized on the surface and that only rarely did the pollen particles penetrate the tunica propria.

Diagnostic Assessment

The complete evaluation of patients with rhinitis demands a systematic approach. Careful collection of personal and family history data and the physical examination supplemented and confirmed by appropriate laboratory evaluation are necessary for accurate diagnosis.

Role of the history

Rapid successions of paroxysms of morning sneezing - generally 10 to 50 sneezes per episode - associated with nasal blockage, rhinorrhea, and itching of the nose, eyes, palate, and pharynx are hallmarks of allergic rhinitis. Other manifestations of atopy, such as infantile eczema, wheezy bronchitis or bronchospasm with exercise and cold, and serous otitis media, may precede the development of rhinitis.

Important clues about what may be causing a patient's allergic rhinitis can be obtained through studying the timing and location of agents that appear to have caused the exacerbation of symptoms. To a significant extent, clinical evaluation of patients is like detective work in that it involves gathering and sorting out clues from various bits of information. The symptoms may be periodic or continuous, depending on the nature of the exposure to the allergen. Symptoms perceived by the patient as being accentuated by increased exposure out-of-doors, particularly on windy days (and especially during the morning and evening hours), and as recurring annually for several years at the same time, strongly suggest an allergic cause. Knowledge of the patient's perceptions can be particularly helpful in the diagnosis when symptoms appear to coincide with the pollination of a known offending tree, grass, or weed - trees usually pollinate in the spring, grasses in the summer, and weed such as ragweed in the late summer and early fall. However, in warmer climates the grass season extends over many months, and mold spores remain in the air throughout the year. The most common perennial allergens are house dust allergens and animal danders. In households with pets, the animal dander contaminates the atmosphere of the entire home, and symptoms can be provoked without direct contact between patient and pet.

Many otolaryngologists - head and neck surgeons use patient history questionnaires to elicit pertinent information systematically. This practice ensures getting a comprehensive history and also provides the basis for detailed questioning in selected areas. Use of such forms not only save times for the practitioner and office staff, but also makes it possible to computerize the information to provide an immediate summary of relevant data for determining the most appropriate laboratory tests. Patients with year-round symptoms, however, present more of a diagnostic challenge than can be met by a questionnaire analysis. Histories in these cases do not contribute as much to the etiologic diagnosis as they do when the conditions are seasonal. In fact, some investigators have questioned the reliability and usefulness of the allergic history, especially in determining the specific cause. In one study of 400 case histories, only about a third were found to be consistent; in half, the histories were variable and confusing; and in the remaining 20%, the histories were of no help at all (Fadal and Nalebuff, 1979). This is not too surprising, since the quality of the evaluation is dependent on many variables in both the examiner and the respondent.

Physical examination

While no characteristic rhinoscopic finding in nasal allergy exists, pale, bluish, edematous nasal turbinates coated with a thin, clear secretion are often found in these patients. Nevertheless, many persons with atopic disease do not have these findings, and the diagnosis cannot be made by appearance alone without confirmatory laboratory findings.

Children with year-round allergic rhinitis can sometimes be recognized by their "allergic salute", in which the palm of the hand rubs the nose in an upward and outward fashion - an indication of nasal pruritus. This constant upward rubbing of the obstructed itchy nose may result in a permanent transverse crease across its lower part, just above the nasal tip. Other frequent findings include abnormalities of the oral cavity with overriding maxillary incisors, a high-arched palate, and hypertrophic lymphoid follicles on the posterior pharyngeal wall. Dark circles under the eyes - "allergic shiners" - as a result of chronic, nonspecific

vascular congestion are common. Transverse creases on the lower eyelid parallel to the lower lid margin are another nonspecific sign of congestion. Tearing and conjunctival injection, lid edema, and periorbital swelling may also be present.

Laboratory Confirmation

Skin tests

For almost a century, when IgE-mediated rhinitis has been suspected, in vivo skin test challenges have been employed to confirm sensitization to specific allergens. The basic principle of these tests is to demonstrate that sensitized mast cells in the skin can be induced by a specific allergen to initiate a local allergic response characterized by a wheal-and-flare reaction. In the various skin-testing methods an allergen extract is placed into the skin by either scratching or pricking with a sharp device or by intradermal injection using a syringe and needle. False-positive skin test results can occur from improper preparation of the allergen material, the intradermal injection of solutions containing concentrations of glycerin (5% or greater), or the intradermal injection of too large a volume of allergen. A test using only diluent solution (0.4% phenolated saline) is usually included to assess skin reactivity resulting from the mechanical trauma as well. Using a 1:100 to 1:500 dilution of a histamine base solution (2.75 mg/mL) as a positive control is also advisable. This helps identify any false-negative skin test result occurring from loss of potency of the allergen solution or prior use of drugs that may suppress skin reactivity. Despite these precautions, factors such as skin responsiveness related to the patient's age, the dampening effect of therapeutic agents, and variables in technique and interpretation limit the accuracy of all skin testing (Fadal and Nalebuff, 1979).

Radioallergosorbent test

The discovery of IgE as the antibody responsible for the classical immediate allergic reaction (Ishizaka et al, 1966) soon led to the development of the in vitro RAST procedure for its detection in serum (Wide et al, 1967). Subsequent modifications in the immunoassay technology (Ali et al, 1982; De Filippi et al, 1981; Fadal and Nalebuff, 1979) have led to the expanding use of RAST by physician to confirm the allergic diagnosis (King, 1982; Nalebuff et al, 1979).

The test is performed as follows: allergen material, chemically linked to a solid-phase support such as a paper disk, is incubated with a droplet of serum from the allergic patient. Allergen-specific IgE antibodies in the test serum bind to the covalently linked insolubilized allergens. Then radio-labeled antihuman IgE antibody raised in another species (rabbit or goat) is added to the allergen disk. The amount of radioactivity remaining bound to the disk after a washing procedure becomes an indirect measure of the specific IgE antibody concentration in the serum being tested.

This immunoassay is capable of detecting serum antibody levels at picogram concentrations, and test results correlate with the allergic history (Aas and Lundkvist, 1973; Evans et al, 1972; Gleich and Yunginger, 1975), the response to allergen challenge (Hoffman

and Haddad, 1974), and the results of skin end-point titration (Norman, 1975). Nearly 90% of children with positive RAST results have manifest allergy as demonstrated by a positive provocation (Berg and Johansson, 1974). However, two thirds of patients with positive intradermal test results and negative RAST results have negative provocation test results. Even the response to drug treatment and immunotherapy can be related to the RAST score (Nalebuff et al, 1981; Welsh et al, 1977).

Nasal smears

Nasal secretions are collected by wiping the nasal cavity with a cotton-tipped applicator, by aspirating with suction or syringe, or by having the patient blow the nose onto waxed paper. The specimens are then treated with either the Wright-Giemsa or Hansel stain and scanned by light microscopy. For years the presence of eosinophils in nasal secretion has been presumed to be a clinical indicator of an allergic reaction in rhinitis patients, and their demonstration has been considered pathognomonic of an allergic diathesis (Hansel, 1966). The eosinophil count is usually performed on a single smear, and the presence of a high number of such cells is interpreted as an additional confirmation of nasal allergy. Pelikan (1983) questioned this technique when he observed that 16% of patients with positive nasal allergen challenge results had a total absence of eosinophils. He detected, however, consequential increases in the number of these cells 30 minutes after allergen challenge and had suggested that only such shifts be accepted as a supplementary diagnostic parameter. Moreover, it is now recognized that, aside from classical allergy, many conditions can lead to nasal eosinophilia; therefore their detection in nasal secretion is no longer considered pathognomonic of atopic disease. In recent years, for example, Jacobs et al (1981), Mullarkey et al (1980), and Zieger and Schatz (1982) have described a form of nonallergic rhinitis with eosinophilia (NARES syndrome) that mimics allergic rhinitis and must be considered in the differential diagnosis.

Management

Once the diagnosis has been confirmed, appropriate treatment may be started. In the management of allergic rhinitis, allergen avoidance by environmental control, pharmacotherapy, and allergen immunotherapy are the major modalities of treatment. When these are properly applied, they lead to acceptable relief of troublesome symptoms in more than 90% of rhinitis patients.

Environmental control

Pollen

No more than 10% of pollen grains may be implicated as aeroallergen sources capable of fulfilling the requirements essential for such material to be of clinical importance (see list below). Goldenrod, for example, is widely distributed and produces an abundance of pollen, yet little gets into the air because it is insect-pollinated and lacks buoyancy. Thus sensitization is limited to people in direct contact with the flowers. The ragweeds, on the other hand, fulfill all five requirements of an aeroallergen. They produce huge amounts of pollen (1 billion

grains per plant), which is spread over several miles by the wind, bringing the risk of exposure to all susceptible individuals in that area. Ambient pollen levels as low as 7 to 20 grains per cubic meter, for ragweed and grass respectively, have been associated with over symptoms in virtually all specifically sensitive subjects (Davies and Smith, 1973).

Thommen's postulates: five requirements for pollens to have clinical importance*

1. The pollen must be allergenic.

2. The pollen must be windborne.

3. The pollen must be produced in large quantities.

4. The pollen must be sufficiently buoyant (between 10 and 50 microm in diameter) to be transferred over a considerable distance.

5. The plant producing the pollen must be widely and abundantly distributed close to the human environment.

* On the basis of a very extensive study of hay fever pollens, Thommen (Coca and Grove, 1931) formulated these postulates by which pollens must be evaluated before considering them as potential offenders in allergic rhinitis or atopic asthma.

Since various pollens are common in the air throughout the year, total allergen avoidance is impossible. Measures can be taken, however, to diminish exposure to pollen. Lawn grass should be kept short, and all gardening chores should be performed by someone other than the allergic person. Some control of indoor exposure can be achieved by keeping doors and windows to the bedroom closed. Electrostatic air filters have been found to be helpful in the home, with or without air conditioning. During peak allergen seasons, if possible, the patient should take his vacations in areas with minimal potential for such exposure; a dry climate with low air pollution and vegetation that produces a small amount of pollen should benefit anyone with allergen sensitivity. Nevertheless, while some patients who change climate do show improvement, a patient should consider a permanent move only after several successful trial periods in the new area. Since allergic symptoms may recur in the new environment because of an acquired sensitivity to allergens unique to the region, permanent geographic moves to change allergen exposures should not be recommended lightly. Furthermore, in most situations economic and social factors mitigate against such transfers.

Mold spores

Outdoor molds are abundant in the grass during prolonged wet periods of the spring. In the fall molds are abundant on fallen leaves. Heavy vegetation around the house should be avoided, since it encourages dampness and mold growth. Inasmuch as molds are mostly a problem in humid areas, controlling heat and dampness will reduce the amount of mold spores inside the house. If a humidifier is used, it should be set to maintain a 40% humidity level within the home. As an aid in identifying mold contamination, mold plates are available

that can be strategically placed at suspicious sites to aid in identifying offenders. Bathrooms are popular havens for mold growth, especially behind the toilet or under the sink - wherever moisture is apt to collect.

Treatment of mold allergy is started by removing all suspicious materials such as upholstered furniture, carpets, and books from the patient's bedroom. Also, there are many mold-inhibiting household products on the market that can be sprayed or painted on walls and in cellars to decrease exposure.

House dust

Probably the most troublesome nonpollen inhalant allergen is house dust, a heterogeneous mixture composed of the breakdown products of common materials found in the home. Whether house dust contains special or unique antigens has been the subject of speculation and research for years. Since 1969 we have known that the major allergenic component of such dust is the house dust mite *(Dermatophagoides pteronyssinus);* these arthropods are found in approximately 80% of house dust samples wherever they are collected (Voorhorst et al, 1969; Wharton, 1970). Mites are especially abundant in the surface dust of mattresses (4000/g), where desquamated human skin scales provide their nourishment (Mygind, 1979). Mattresses and box springs, especially those containing cotton fillers, have been called the "giant graveyard of mites". Feathers in the patient's pillow have often been accused of causing symptoms in rhinitis patients, but it seems unlikely that a specific feather allergen is a major offending substance. In fact, Wormald (1971) believes that 96% of all positive skin test results with "feather allergen" are a result of mite infestation.

Several measures are effective in lowering the mite population. During housecleaning mite allergens become airborne in large quantity and remain in the air for some time; much of the allergen is in particles about the size of pollen grains (Baer, 1983; Tovey et al, 1981). Control of bedroom dust is obviously important in house dust-sensitive patients. Floors should have a hard surface and not be carpeted. Curtains should be washable, and bedroom closets should be used only for the storage of clothing. Cotton mattresses or box springs can be replaced by foam rubber encased in allergenproof casings. After conducting a trial of avoidance measures aimed at reducing exposure to mite allergen, Sarsfield (1974) concluded that the single most important step is the covering of the mattress with a plastic cover. Down blankets and feather pillows may also be replaced with polyester blankets and synthetic foam pillows, which are less hospitable to mites. Bed linens should be changed three times a week, and the mattress vacuumed once a month. Rao et al (1975) studied the mite populations in mattress dust from hospitals and private houses; whereas an analysis of mattress dust from 100 hospital beds showed that 94 were mite free, all 50 mattress dust samples taken from private homes were mite infested. They assumed that the frequent changing and washing of bed linen and brushing and cleaning of mattresses in the hospital setting were the main factors in preventing mite infestation.

Animal dander

In cases of animal dander allergy no form of treatment is as effective as eliminating the source. However, getting patients to comply is often impossible - even when the symptoms include disabling asthma. At the very least, carpets made of animal hair and animal skin rugs should be removed from the patient's home and work environment. Patients known to be atopically sensitized to the dander of one animal should avoid other furred or feathered animals, since they are likely to develop sensitization to these as well. Those individuals whose livelihood depends on continuing contact with animals should be advised to use masks and protective clothing.

Pharmacotherapeutic approaches

Direct costs to patients for medication and treatment of allergic rhinitis total well above $250 million annually, and indirect costs exceed $500 million (NIAID task force report, 1979). This disease is estimated to be responsible for 10 million days lost from work, 8 million office visits to physicians, and 6 million bedridden days per year.

Despite the frequency of pharmacologic intervention, no single medication can cure allergic rhinitis. Several types of drugs, however, do serve a useful role in the care of allergic rhinitis patients. The antihistaminics, for example, accounted for approximately 7% (almost 44 million) of all prescriptions in 1981.

Antihistaminics

The initial pharmacologic management of allergic rhinitis should begin with the antihistamines of the H1 class. They antagonize histaminic action by competing for receptor sites on target cells; premedication with these agents - before histamine-liberating evens - preempts available receptors and affords optimal blockade. Thus these drugs should be administered at the onset of symptoms and continued on a regular basis until symptoms are controlled or until the side effects of the medication become intolerable. In recent years a new class of nonsedating antihistaminics have become available and have been found to be effective in providing symptom relief (Table 44-2).

Other preparations that are clinically effective but cause sedation and are therefore limiting at other times are acceptable for use at bedtime. Such antihistaminics taken at bedtime (especially in "time-release" form) often help mitigate symptom peaks that occur on arising. Because of variable individual response to medication among patients, the physician should be familiar with agents from each of the major classes of antihistamines.

Decongestants

The oral decongestants pseudoephedrine and phenylpropanolamine may be effective in managing allergic rhinitis that manifests itself primarily by symptoms of congestion. However, they are frequently unsatisfactory because of the side effects of excessive stimulation and insomnia. These drugs are often more effective when used in conjunction with

an antihistaminic, since a useful synergism exists between the two components - the action of the stimulating decongestant usually minimizes the sedative effect of the antihistaminic.

More subtle adverse effects, especially in elderly or chronically ill patients, include modest rises in blood pressure, cardiac irritability, constipation, urinary retention (particularly in male patients), and precipitation of acute glaucoma. Patients taking medications for nasal complaints rarely mention these symptoms, and so the physician must be especially diligent in asking about them.

While topical decongestants preclude systemic side effects, they may nevertheless induce rebound symptoms that seriously limit their usefulness in the routine management of all but the most acute episodes of rhinitis.

Table 44-2. Antihistamines*

Class	Trade name	Effects
Alkyamines	Actidil Chlor-Trimeton Co-Pyronil Dimetane Polaramine Teldrin	Low sedative, anticholinergic, and gastrointestinal effects
Amino-alkyl ethers	Benadryl Naldecon Rondec Tavist	High sedative effects; moderate anti-cholinergic effects; infrequent gastrointestinal complaints
Ethylenediamines	PBZ Rynatan Triaminic	Low sedative and anticholinergic effects; gastrointestinal complaints are common
Miscellaneous	Atarax Optimine	Drowsiness is common
	Periactine	Useful in treatment of urticaria
Nonsedating agents	Hismanal Loratadine Seldane	Sedation, impaired coordination, and other signs of CNS depression do not occur
Phenothiazines	Phenergan	Pronounced sedative effect
	Temaril	Useful in treatment of itching.

* The most commonly used antihistamines are listed. Although all are similar in pharmacologic activity, in patients whose allergy is poorly controlled with one preparation, switching to another class may be beneficial.

Corticosteroids

In some instances a patient's symptoms may not respond to the above measures and may be so severe as to necessitate therapy with corticosteroids. Physicians for years have attempted to avoid the systemic side effects of corticosteroids by using topical hydrocortisone, prednisolone, and dexamethasone phosphate (Decadron Turbinaire). Although these agents can control rhinitis, they have the potential for causing substantial adrenal suppression, since about 30% of an average dose is absorbed systemically. Topical use of these medications, therefore, should be restricted to a maximum of 6 weeks.

In recent years the corticosteroids beclomethasone dipropionate (Beconase or Vancenase) and flunisolide (Nasalide) have become available as aerosols. Even when used in small doses, they have potent local effects. When these preparations are sprayed into the nose in doses of 400 microg daily, they can effectively control the main symptoms of rhinitis in 75% to 90% of patients. When the patient gets satisfactory relief, usually from 3 to 10 days following initiation of treatment, the dosage can be gradually reduced to the lowest possible maintenance level (Parkin, 1983). Significantly, in studies in which these preparations were given by the nasal route at doses of 200 to 1000 microg, patients exhibited no adrenal suppression. The main adverse reactions reported were aerosol-induced sneezing, transient burning, and stinging.

Another method of administering steroid therapy is by intraturbinal injection. Mabry (1983) used this form of treatment with success in over 7500 patients and found it to be an effective tool where other conservative measures had failed. Injections given once or twice a year can alleviate symptoms throughout the involved pollen's season. Two percent of patients experience such adverse side effects as nasal bleeding and facial flushing. Intranasal steroid injection does present one possible catastrophic complication: visual loss. The mechanism of injury appears to be retinal embolization or vasospasm, and a total of 11 such case have been documented. Those expert in this treatment method believe that careful attention to technique precludes this complication.

While using systemic steroids in long-term rhinitis is not warranted, topical or systemic steroids are very useful in treating severe nasal allergy of short duration. Strikingly beneficial effects can be obtained from either of the following two methods of treating with corticosteroids:

1. Oral prednisone given as a short bursts in a high initial bolus (40 to 80 mg) followed by a gradual tapering of the dose of 10 mg on alternate days over a period of 7 to 14 days.

2. A single injection of triamcinolone intramuscularly (eg, 40 to 60 mg Kenalog).

Use of corticosteroids in this fashion, either alone or with other medications, not only provides excellent results, but also may obviate the need for long-term allergen immunotherapy and its concomitant expenditure of time and money for the patient.

Cromolyn sodium

In 1967 Altounyan demonstrated that the inhalation of cromolyn sodium prevented bronchoconstriction following allergen provocation. That this drug was neither a bronchodilator nor an antagonist of the chemical mediators is now evident. Nevertheless, this disodium salt of cromoglycic acid prevents the allergen-antibody reaction from triggering mast cell degranulation and the release of the symptom-provoking mediators. It has also been shown to reduce non-IgE-mediated mast cell degranulation induced by certain chemical compounds, drugs, or other substances and to prevent asthma induced by exercise and neurogenic mechanisms. Allergic reactions of the reaginic type occurring in the nasal mucosa can be blocked by pretreatment with cromolyn just as similar reactions are inhibited in the bronchial mucosa of asthmatic patients. Handelman et al (1977) found that cromolyn sodium solution is effective in reducing sneezing, rhinorrhea, nasal congestion, and ocular irritation in patients with ragweed hay fever. Pelikan and Pelikan-Filipek (1982) concluded that intranasal cromolyn used as a 4% solution is the drug of first choice to control the symptoms of allergic rhinitis.

As physicians have gained experience with the effectiveness of nasal cromolyn, it has become apparent that appropriate candidates must be identified through proper differential diagnosis of the other forms of rhinitis (see Chapter 45) and that cromolyn must be administered before challenge.

Allergen immunotherapy

When environmental control and pharmacologic therapy fail to provide rhinitis patients with relief and symptoms have lasted for more than 2 years, allergen immunotherapy may still be effective in relieving symptoms. Furthermore, this form of treatment is the only one that offers the hope of "cure". Proven clinical benefits of immunotherapy have been reported in such treatment-resistant patients suffering from allergic rhinitis caused by ragweed, grass, mountain cedar and birch pollen, house dust, and mite and cat dander sensitivity. Indications for initiating such therapy are as follows:

1. The patient responds inadequately to environmental control measures and pharmacotherapy.

2. Inhalant allergens via IgE mechanisms trigger the treatment of allergic rhinitis.

3. The severity, duration, and frequency of symptomatic episodes are more of a problem than the inconvenience and costs involved with immunotherapy.

4. The patient is likely to comply with the schedule of periodic injections for up to several years.

Various approaches

Allergen immunotherapy is usually carried out by one of three methods: the traditional technique, the skin end-point titration approach, or the RAST-based method.

Traditional technique. In this method an arbitrary safe dose of allergens is administered in relatively high dilutions (1:100.000 to 1:1.000.000 weight per volume). Dosage is increased once or twice a week over several months until a maintenance dose of allergen is reached. Because therapeutically effective doses are not reached until 6 to 12 months, some physicians accelerate the traditional schedule by administering doses several times a day - a variation called *rush therapy.* The inherent disadvantage of this traditional method is that the physician must rely on the patient's history and the skin's response to but a single dilution of test antigen to determine the degree of sensitivity.

Skin end-point titration approach. In this method the starting dose advocated is approximately 10 time the volume of allergen required to cause a positive skin-test reaction, and treatment doses are increased incrementally until an ultimate maintenance level is reached. This level may be several thousand times the amount of allergen found to cause the end-point response. In addition, the amount of each allergen in a treatment mixture is individually determined by bioassay to be inversely related to patient sensitivity as determined by the skin's response to allergen challenge.

Rast-based method. With RAST the starting immunotherapy dose is based on the serum level of allergen-specific IgE antibody. When more than one allergen is mixed in a treatment vial, the various allergen concentrations are adjusted in inverse proportion to their individual serum antibody concentration. Thus, as incremental doses proceed, there is little likelihood of adverse reactions occurring during the course of treatment. When this approach is used, the initial dose of allergen often can be higher than that of the two other methods, making it feasible to reach therapeutically effective levels promptly, usually within a month or so (Nalebuff et al, 1979).

Immunologic changes associated with immunotherapy

While the clinical efficacy of specific allergen immunotherapy as an adjunct to the management of patients with seasonal allergic rhinitis is well documented (Johnstone, 1957; Norman, 1978; Pruzansky and Paterson, 1968; Sadan et al, 1969), the extent to which any given patient responds remains unpredictable. Furthermore, few patients receive enough benefit from this modality to enable them to discontinue all medication. Permanent relief is rare, and once therapy is discontinued, the patient may suffer a relapse.

The major advantage immunotherapy has over other treatments is its precision; that is, the patient experiences relief for administered allergens only. Symptoms caused by other allergens do not change during therapy. Research studies confirming the efficacy of allergen immunotherapy demonstrate that high doses of allergenically active material must be administered to produce immunologic changes in most clinically improved patients. These changes are described below.

Decrease in skin reactivity. In a 1954 study Frankland and Augustin reported that patients treated with potent extracts had consequential diminution in the skin reactivity, as compared with such responses noted at the onset. They found no such responses in a group of patients treated for the same length of time with inactive material or placebo. In 1978 Taylor et al treated sensitive patients with cat dander allergen and demonstrated a significant decrease in skin reactivity as compared with a placebo-treated group.

Changes in specific IgE antibody. Connell and Sherman (1964) observed that, after an initial elevation, serum levels of IgE taper off and, after 1 or 2 years, fall below original levels. The researchers also observed that the expected seasonal rise in specific IgE titers found in untreated atopic patients is suppressed in treated patients.

Changes in specific IgG antibody. The concentration of specific IgG antibody rises markedly in the first few months after allergen immunotherapy is initiated and soon reaches a plateau despite continued increases in antigen dose. The magnitude of the increase is dependent on the dose of allergen administered. Of all the immunologic changes that have been described, the one that correlates best with clinical improvement is the generation of allergen-specific IgG antibody. This correlation is especially evident in venom immunotherapy, where achieving increased levels of IgG antibody correlates with protection. This same relationship has recently been reported for ragweed and grass-induced rhinitis (Ali et al, 1983; Creticos et al, 1984).

Changes in cell sensitivity. By calculating the concentration of allergen required to release 50% of the histamine contained in blood basophils, one often observes that cells from treated patients become significantly less reactive to antigen challenge than similar ones taken from untreated patients (Levy et al, 1971).

Lymphocyte alteration. Immunotherapy can bring about changes in both lymphocyte proliferation and the production of lymphokines when challenged with allergen (Rocklin, 1983). Mononuclear cells from ragweed-sensitive patients exhibit a meaningful proliferative response when cultured with ragweed antigen. After specific therapy, diminished proliferative responses have been observed, as well as a decrease in the production of at least two cell products: the macrophage inhibition factor and the lymphocytic mitogenic factor. Since cells cultured in either autologous or homologous serum are similarly affected, this decrease in antigen-specific lymphocyte responsiveness is not dependent on the presence of a serum factor induced by immunotherapy. In addition, changes in the lymphocyte surface markers have been observed in atopic patients after specific immunotherapy. Untreated atopic patients have fewer T cells bearing Fc receptors for IgG as compared with normal controls. As a result of therapy, the proportion of T cells bearing such receptors has increased to normal levels.

Length of treatment and prognosis

For patients receiving allergen immunotherapy, the usual recommended course of treatment is from 3 to 5 years. Such therapy should be discontinued, however, if after 3 years of uninterrupted maintenance the patient shows no clinical improvement. If the patient has not responded in that amount of time, he probably will not do so should immunotherapy be continued. Many patients with seasonal rhinitis tend to improve spontaneously with time; however, those with perennial symptoms usually do not. Nevertheless, most patients do respond favorably to proper comprehensive medical care. As a rule, one finds an 80% to 90% reduction in symptoms in such a treated patient. One must be sure, in those not responding, that other forms of rhinitis are not coexisting and that any physical factors contributing to symptoms, such as septal deviations and turbinate enlargements, are corrected.