ALLERGIC RHINITIS

A Common Illness and Paradigm For IgE-Mediated Processes

Internal Medicine Grand Rounds

August 27, 1992

Parkland Memorial Hospital

The University of Texas Southwestern Medical Center at Dallas

Donald Kennerly, M.D., Ph.D.

HISTORICAL PERSPECTIVE

Allergic rhinitis is a disorder of modern man. Unlike many diseases that can be traced to detailed ancient clinical description, allergic rhinitis was not described until 1819 when Bostock first observed the occurrence of seasonal rhinitis in England. During the ensuing years of Bostock's career he was able to assemble only several dozen cases of seasonal rhinitis despite an active interest in the disorder. The next major advance in allergic rhinitis took place in 1841 when Elliotson first proposed that plant pollens might cause seasonal rhinitis.

Along a different line, Von Recklinghausen first described the existence of granulated cells in dissected mesentery. However, it wasn't until 1878 that Paul Ehrlich first described the metachromatic staining pattern of "mastzellen" -- mast cells as we call them today.

From a clinical perspective, Blackley brilliantly described and documented for the first time in 1873 that pollen caused his own seasonal rhinitis. By introducing pollen into his nose he was able to produce nasal congestion, rhinorrhea and sneezing. Perhaps more impressively, Blackley performed the first meaningful allergy skin test when he showed that placing pollen grains on his arm and scarifying the area caused the development of an immediate wheal and flare response while a similar procedure in the absence of pollen failed to produce any reaction on the contralateral arm. This work unfortunately did not take hold at the time. In 1906 Von Pirquet coined the term "allergy" which he defined as the altered capacity to react. During this time of active interest in immunization for bacterial and viral diseases, immunotherapy for allergic diseases evolved and it was Noon in 1911 who first described a course of immunotherapy for seasonal rhinitis.

Also in 1911 Dal described the physiological impact of histamine on the vasculature but it was to be more than 40 years before mast cells were shown to contain histamine. In 1921, passive transfer of immediate type hypersensitivity was first demonstrated by transferring serum from a patient with fish sensitivity to a nonallergic recipient. The field lay relatively fallow of major investigations but evolution of skin testing, the aerobiology of pollens and desensitization took place during the 1920-1960 period. In 1937 Bovet developed the first H1 antihistamine; the first pharmacologic treatment of allergic rhinitis. In 1953 Riley ad West demonstrated for the first time that mast cells contain histamine and thereby provided the footing for the modern study of mast cells and their role in immediate hypersensitivity responses. In 1967, the Ishizaka's published their characterization of IgE antibody (reaginic antibody) and demonstrated its specific binding to tissue mast cells and circulating basophils; ushering in the modern era of immediate hypersensitivity.

During the ensuing 15 to 20 years investigative efforts have focused upon two major areas in immediate hypersensitivity in the basic science arena. First, isolation and purification of mast cells by a number of investigators made it possible to study the detailed intracellular biochemical processes that take place in mast cells stimulated by cross-linking IgE receptors. Second, and more recently, the regulation of the IgE immune response has become an intense area of investigation and has provided very important insights from both scientific as well as clinical perspectives. With emerging structural knowledge of IgE and its high affinity receptor (FcϵRI), a more complete understanding of the biochemical pathways important in mast cell activation and the ability to use molecular approaches to antagonize unwanted biochemical and

cross-linking IgE receptors. Second, and more recently, the regulation of the IgE immune response has become an intense area of investigation and has provided very important insights from both scientific as well as clinical perspectives. With emerging structural knowledge of IgE and its high affinity receptor (FcϵRI), a more complete understanding of the biochemical pathways important in mast cell activation and the ability to use molecular approaches to antagonize unwanted biochemical and immunologic processes, we are currently entering a time when the control of allergic disorders will be increasingly successful. During the next 1-2 decades it is quite possible that we may bring to a close the major morbidity that allergic rhinitis brings to a large fraction of those living in the industrialized world.

EPIDEMIOLOGY/IMPORTANCE

Allergic rhinitis is the most common chronic disease of young adults. A recent survey of more than 10,000 Americans revealed that 17.5% of Americans (over 40 million individuals) are afflicted by allergic rhinitis (Hess + Lyon, 1985). Figure 1 demonstrates that the incidence of allergic rhinitis increases rapidly in childhood, reaches a maximum in young adulthood and middle age and declines in the over 50 age group. Approximately 80% of patients who ultimately develop allergic rhinitis first experience symptoms by the age of 25 (Smith, 1984). There is no preference for race, sex, or ethnic background.

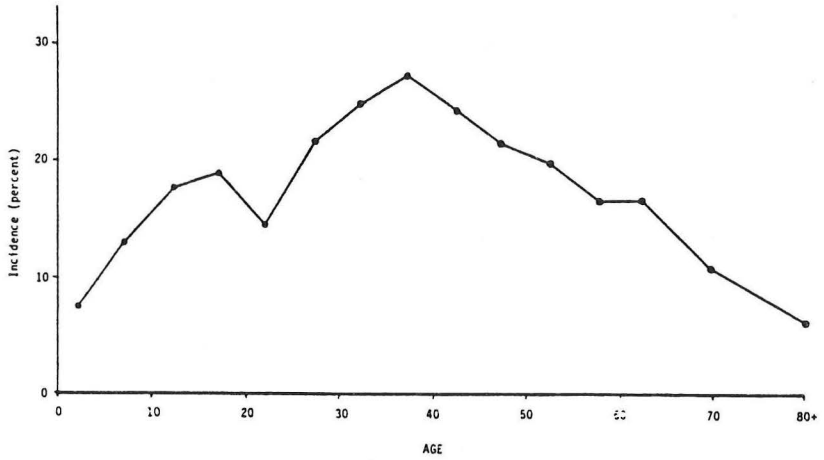

FIGURE 1

Allergic rhinitis is primarily a disorder of industrialized highly developed nations such as our own and those of Europe and Japan (Smith, 1984). In less developed societies there is a much reduced frequency and it would appear that the absence of a clinical description of this disease prior to the 19th century suggests that it is a disorder associated with improved sanitation. There is considerable controversy and interest in the theory that parasitic infection in underdeveloped societies "diverts" the IgE immune response from responding to pollen and other aeroallergens that are present in nearly all nations. It seems ironic that the ability to mount a brisk IgE response for millennia probably endowed individuals with a selective advantage in dealing with parasites but in the relatively parasite-free modern environment this population is likely handicapped by atopic disorders.

Figure 2 illustrates epidemiologic data from one region in Japan that indicate that the incidence of allergic rhinitis appears to increasing. A factor strongly correlating with the prevalence of the illness is the presence of pollution; more specifically the generation of particulate material. A statistically significant association of allergic rhinitis and/or asthma with the encroachment of pollution in urban and suburban environments has been confirmed in two other continents as well. The hypothesis that inhaled particulate material may act importantly as an adjuvant in favoring the development of an IgE immune response is obvious and is the subject of work by several groups.

The atopic diathesis is transmitted genetically in an autosomal dominant fashion with

variable penetrance. The risk of developing allergic rhinitis is approximately 30% if one parent has an atopic disorder (Smith, 1984).

Cedar-Induced Allergic Rhinitis
(Nikko-Imaichi, Koizumi)

Rate		Year
3.8%	(45/1183)	1974
5.8%	(77/1332)	1977
9.8%	(306/3133)	1984
16.3%	(303/1862)	1986

FIGURE 2

The cost to the American public of this disorder is considerable. The annual cost in physician's services, medication, and lost time from work is approximately $3 billion and the value of nearly 3 million missed school days cannot be estimated.

For a variety of reasons allergic rhinitis tends not to be treated as successfully as many other illnesses. Perhaps because the symptoms that accompany this illness are not life threatening, both patients and physicians tend not to make its effective treatment a priority. A recent survey indicates that only 75% of individuals affected by allergic rhinitis take any medications. Many patients continue to seek relief with over the counter medications that frequently incur sufficiently significant side effects that their use is limited to times when they are truly miserable. The increasing recognition by the public that nonsedating antihistamines are available (with their resultant capture of the majority of the H_1 antagonist prescription market) has tended to encourage patients to seek medical care for this illness. An additional factor that limits the successful therapy of patients with allergic rhinitis, particularly those with moderate to severe symptoms, is the lack of adequate allergy training during most residency training programs, given their focus on more severe illnesses that are managed on inpatient services.

Further emphasizing the need for appropriate management are striking data from the Mayo Clinic that appropriate therapy of seasonal allergic rhinitis with topical nasal glucocorticoids results in marked coseasonal reduction in seasonal asthma induced by exposure to relavent allergens. Data also data indicate that the isolated nasal allergen challenge results in increased bronchial hyperreactivity. Thus, while allergic asthma receives greater attention in patients as the result of its more serious mobidity and mortality, failing to treat allergic rhinitis may have important consequences.

PATHOPHYSIOLOGY

Nasal Function

Figure 3 summarizes the roles of the nose in human physiology. In addition to providing the respiratory airway in children and in non-exercising adults, the nose is important in warming, humidifying and filtering the air we breath. It provides the lower respiratory tract with nearly 10,000 liters per day of humidified warm air that is largely depleted airborne of particles. Despite ambient temperatures from 0-25°C, the nose and nasopharynx is able to provide the lung with air warmed to 36-37°C. By producing approximately 1 liter of nasal secretions per day, the nose provides the lower respiratory tract with air at 75-95% relative humidity (Proctor, 1983).

FUNCTION OF THE NOSE

Airway (children and resting adults)

Conditioning of air
- warming
- humidification
- filtration

Protection of lower respiratory tract (filtration/reflexes)

Olfaction

Vocal resonance

FIGURE 3

As illustrated in Figure 4, the vibrissae and mucocilliary clearance mechanism effectively remove the vast majority of particles greater than 10 microns in diameter and 80% of those in the 5-10 micron range (Muir, 1972). Because of turbulent flow in the nose, particles impact on the mucocilliary blanket, are trapped by physical or electrostatic forces and are removed by subsequent posterior movement of the mucus blanket by ciliary transport. Fifteen minutes is a typical "transit time" from anterior nasal mucosa to nasopharynx (Proctor, 1973). Cultures at different location in the nose reveal that there are few bacteria in the posterior choana and the sinuses are usually sterile. In the anterior portion of the nose, mucocilliary transport is slow but in the posterior regions rates of 60 cm/hr are achieved. Irritating pollutants such as sulphur dioxide cause a marked reduction in ciliary transport (40% of normal at 1 part per million) (Anderson et al., 1974).

Nasal Physiology

The nose responds to multiple physiologic signals including hormones, neurotransmitters, and physical stimuli; a topic that is exhaustively described elsewhere (Mygind, 1982). Figure 5 schematically presents the microscopic anatomy of the nose.

The normal mucosa is composed of columnar epithelial cells that possess either microvilli or cilia and occasional goblet cells. In patients with allergic rhinitis, there is a substantial increase in the frequency of epithelial mast cells. Numerous glands present in the lamina propria secrete watery fluid. Mast cells are richly represented in perivascular areas.

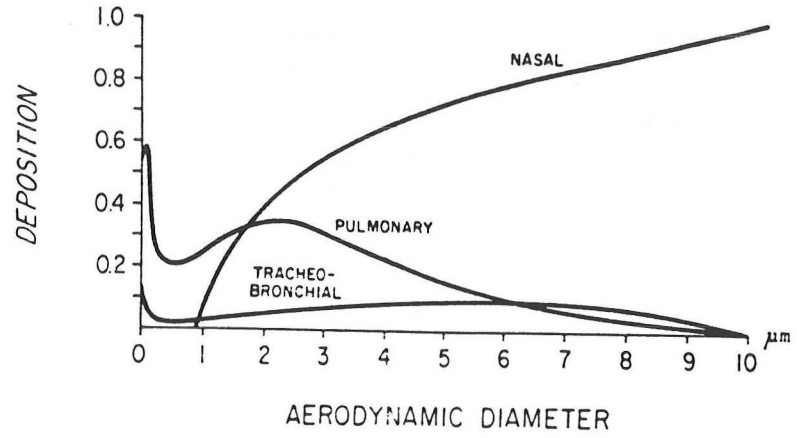

FIGURE 4

The nasal vasculature is important in the regulation of nasal airway resistance (Figure 6). In addition to normal tissue perfusion, the nasal mucosa is rich in capacitance beds (venous sinusoids). When these sinusoids become engorged, there is a marked reduction of the patency of the nose to air flow. The nose is innervated by sympathetic nerves that travel from the stellate ganglion to the nose along blood vessels. Release of norepinephrine produces marked alpha-mediated vasoconstriction while beta 2 stimulation produces mild vasodilatation. Baseline tone is provided primarily by alpha stimulation; a concept supported by the observation that section of the vidian nerve results in marked swelling of the tissue as a result of vasodilation of vascular sinusoidal structures. Antihypertensive agents that interfere with alpha stimulation (guanethidine, bretyllium, aldomet, and reserpine) not infrequently produce nasal congestion as a side effect.

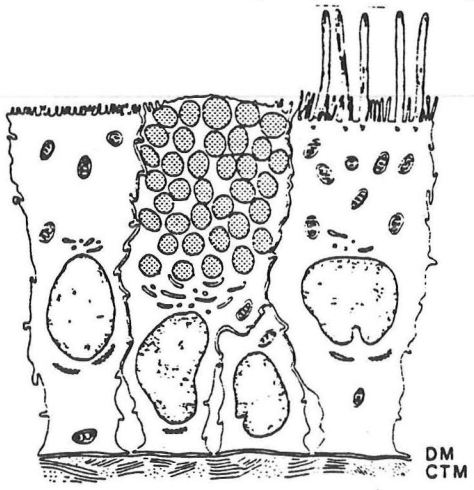

FIGURE 5

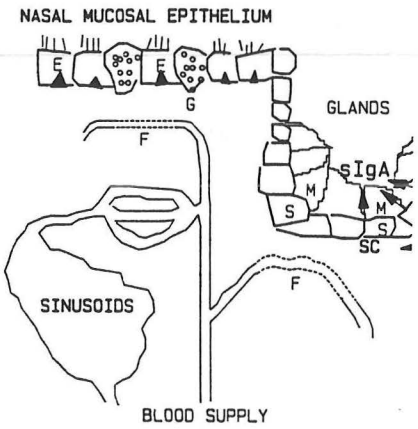

FIGURE 6

Parasympathetic innervation is provided by the facial nerve via the pterygopalatine ganglion. The submucosal glandular tissue is richly innervated by cholinergic parasympathetic post-ganglionic fibers. Stimulation of these nerves results in marked watery rhinorrhea and mild vasodilation (Mygind and Malm, 1982). Anticholinesterases used in the treatment of myasthenia gravis may cause troublesome rhinorrhea by inducing a greater baseline cholinergic tone.

Normally there is an alterating cyclic of obstruction to air flow from one side of the nose to the other over a 2-6 hour time period termed the "turbinate cycle" (Stoksted, 1953). The importance of this cycle is uncertain, but it is postulated top permit the nasal mucosa of the obstructed side to recover in preparation for the high rate of fluid production required to humidify air the portion of the cycle in which airflow over the turbinates takes place (Ritter, 1970). In the absence of air flow (after tracheostomy, for example) this cycle ceases.

Reflexes are important in maintaining nasal homeostasis. A variety of agents including cold temperature, dust, noxious gases and histamine cause stimulation of afferent fibers that pass in the trigeminal nerve resulting in rhinorrhea caused by enhanced parasympathetic output. This represents a protective response to prevent introduction of noxious agents into the lower respiratory tract. Controversy exists as to whether these reflexes become exaggerated (hyperreactive to a similar stimulus) during periods of pollen exposure for patients with allergic rhinitis. Whether such a response is brought about by neuronal hypersensitivity, enhanced epithelial permeability or alterations in the density of relevant receptors for mediators is uncertain.

Mediators of Nasal Allergy - Overview

It was not until 1878 that Paul Ehrlich in his doctoral dissertation described the metachromatic staining of mast cells ("mastzellen"). 75 years passed before it was proven by Riley and West in 1953 that mast cells contain histamine. For nearly 50 years it has been known that mast cell-containing cell suspensions are able to release a material causing a prolonged contraction of guinea pig ileum smooth muscle and was for many years termed SRS-A (slow reacting substance of anaphylaxis). In the late 70's and early 80's, following Parker's discovery that arachidonic acid was a substrate in the formation of SRS-A (Jakschik et al., 1977), work became accelerated and lead to Samuelsson's description of the structure of what we now term the leukotrienes (Murphy et al., 1979). Prostaglandin D_2 (PGD_2) formation by the mast cell was shown in the 1970's by several groups and shown in the purified human mast cell in 1982 (Lewis et al., 1982). Recent work by a number of groups has focused upon the growth and differentiation of mast cells. In addition to IL-3, the critical role of a growth factor variously termed c-*kit* ligand and *stem cell factor* in the growth of mast cells has given considerable additional momentum to this area of investigation. Further, it has been clearly shown by a number of groups that a differentiative spectrum of mast cells exist (the classification scheme and clinical relevance of which is beyond the current discussion) and that the mast cell phenotype is regulated by exposure to these cytokines as well as tissue specific factors.

Mast cell- and basophil-derived inflammatory mediators fall into two categories: those that are preformed and released by exocytosis and those that are newly synthesized at the time of stimulation. Figure 7 illustrates the most important of the mast cell-derived mediators and some of their physiologically relevant effects.

Histamine. In 1911 Dale first described the effect of histamine upon the vasculature. Since that time investigators have focused a great deal of attention upon the importance of this pivotal mediator in immediate hypersensitivity reactions and is formed by the decarboxylation of histidine by histidine decarboxylase. Histamine is stored in electron dense secretory granules in the mast cell in an insoluble ionic lattice bound to anionic polysaccharides. In rodent mast cell granules, the concentration of histamine is approximately 0.4 M (Rabenstein et al., 1985). Although the human mast cell is less robustly armed with histamine, the observation that systemic antihistamines are only modestly effective should not be entirely surprising given the likelihood of high micromolar to low millimolar concentrations of histamine in the vicinity of a stimulated mast cell.

Biological Effects of Mast Cell Activation

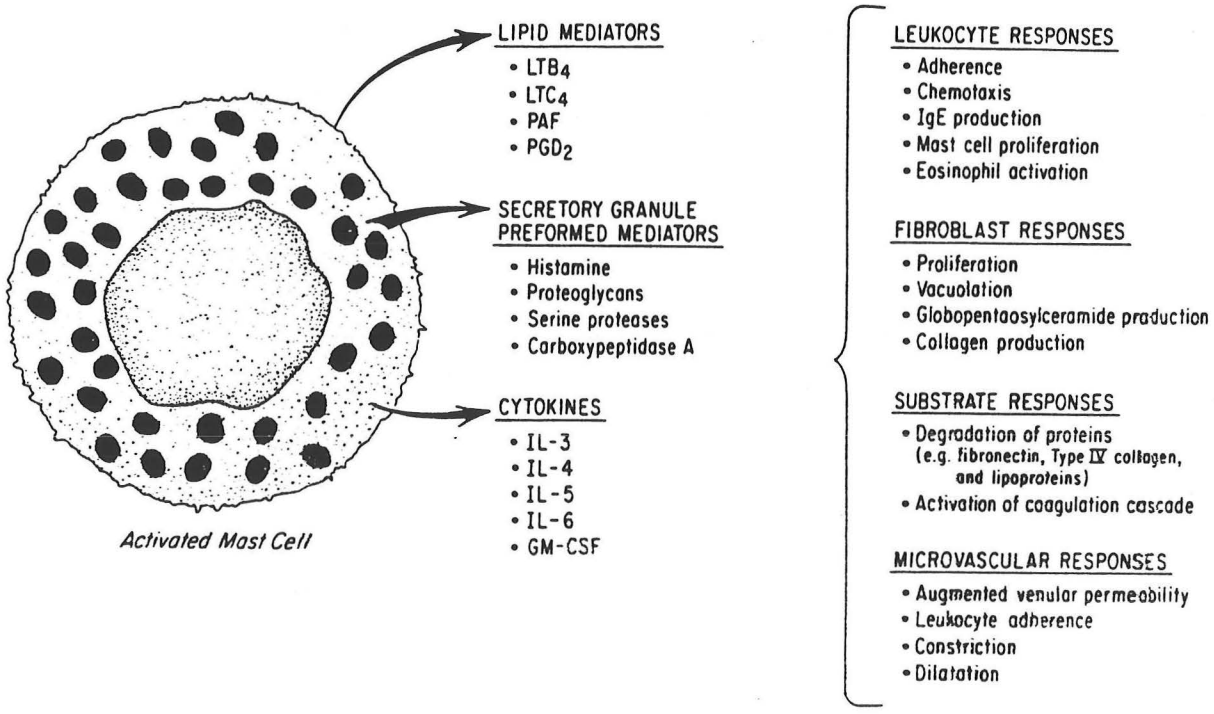

FIGURE 7

Introduction into the nose of aerosols containing histamine produces sneezing, pruritus, obstruction and watery rhinorrhea. Histamine acts directly by an H_1 mechanism on the local vasculature (causing small arteriolar and small venular dilation and increased permeability of post capillary venules). The net result is profound nasal obstruction due

to both engorgement of venous sinusoids and interstitial edema cause by increased vascular permeability. The increase in vascular permeability causes significant loss of plasma proteins and fluid. H_2 vascular mechanisms are modest but H_2 antagonists do modestly improve the inhibition achieved by H_1 antagonists of histamine-mediated nasal obstruction.

In addition to these direct histaminergic effects, this mediator can also initiate the parasympathetic reflexes described previously. Unilateral introduction of histamine produces interesting effects. The minimal and transient contralateral nasal obstruction indicates the lack of a significant role for reflex-mediated obstruction. Secretion on the contralateral side, however, is approximately 60% of that observed on the homolateral side. That this contralateral secretion is blocked effectively by homolateral topical H_1 antihistamines supports the concept that sensory fibers seem likely to be H_1 responsive (Mygind, 1982). Thus, histamine is able to cause rhinorrhea by direct vascular mechanisms and by reflex-mediated glandular hypersecretion.

Prostaglandin D_2 (PGD_2). AFter arachidonic acid is released from mast cell lipid stores it is rapidly converted via cyclooxygenase and subsequent enzymes to produce PGD_2 (Lewis et al., 1982). This prostaglandin is the major cyclooxygenase product in the mast cell and has important physiologic effects including enhancement of vascular permeability. The basophil, however, is not to be able to synthesize PGD_2.

Leukotriene C_4 $(LTC)_4$ - LTC_4 is formed from arachidonic acid by the sequential actions of 5-lipoxygenase (forming LTA_4) and glutathionyl-S-transferase (LTA_4 + glutathione ----> LTC_4; Lewis and Austen, 1984) by human mast cells (MacGlashan et al., 1982). It is able to cause direct enhancement of mucous secretion and increased vascular permeability. Unlike the lung, the ability of LTC_4 to cause smooth muscle contraction is of virtually no importance in the nose.

Kinins - Bradykinin is formed by the action of a mast cell kallikrein present in and released from the granule (Newball et al., 1975). It may be that mast cell neutral proteases are in part responsible for the conversion of kininogen to bradykinin. Kallikrein is assayed in nasal secretion by its ability to catalyze the liberation from the artificial substrate TAME (tosyl arginine [(^{3}H-methyl) ester]) of labeled methanol. Kinins can markedly enhance vascular permeability in a variety of systems.

Other newly formed agents include the arachidonic acid derived thromboxane B_2 (TXB_2) which may be important in platelet activation as is newly formed platelet activating factor (PAF or AGEPC) which is similarly able to cause platelet activation but also causes a direct increase in vascular permeability, eosinophil chemotaxis and activation. Additional evidence that the mast cell is activated as the result of pollen exposure is the appearance of the mast cell-specific and granule-associated enzyme tryptase in lavage fluids from patients challenged with relevant antigens to which they are sensitive.

Mast cell derived cytokines - A very important recent finding by Plaut and Paul is that mast cells are rich sources of a variety of cytokines. Although it is less clear in the

human than in rodent models that T cells can be categorized into T_{H2} and T_{H1} subtypes, the mast cell is able to generate substantial quantities of interleukins and other inflammatory cytokines of that are typical of the T_{H2} subclass (IL-3, IL-4, IL-5, IL-6, GM-CSF and TNF_{α}). Although the production of these cytokines is likely to be of somewhat greater importance in the development and maintenance of asthma, the ability to recruit and activate a variety of inflammatory cells may be important in the expressions of symptoms of allergic rhinitis.

Mechanisms of Mast Cell Mediator Release and Formation

Overview - Although Prausnitz and Kustner in 1921 were able to show passive transfer of immediate hypersensitivity by cell free serum samples, it was not until 1967 through the painstaking and brilliant efforts of the Ishizaka's that IgE was isolated and characterized (Ishizaka and Ishizaka, 1967). Mast cells and basophils alone express the high affinity receptor for IgE (FcϵRI) and recent work has successfully characterized and cloned this three subunit membrane protein that requires the successful expression of all three components for synthesis. It was shown that crosslinking IgE receptors (as a result either of antigen recognition by the bound IgE of interaction of exogenous anti-IgE with cell associated IgE or of exogenous addition of anti-FcϵRI antibody) was able to trigger mast cell secretion in vitro and in vivo.

IgE - IgE is present in human serum at the level of approximately 100 nanograms per ml but because of the very high affinity of the IgE receptor, mast cell and basophil receptors have a high rate of IgE occupancy. IgE antibody is structurally similar to IgG with the exception that the two heavy chains possess an additional constant region resulting in a molecular weight of 190,000 daltons (12% of which is carbohydrate).

Of considerable interest is work by Baird's group showing that IgE binds to FcϵRI at a point at the junction of C_{H2} and C_{H3} domains of the epsilon heavy chains. Further, structural studies demonstrate that the heavy chains of receptor bound IgE bear a more lateral orientation than many had expected (Figure 8). Of clinical relevance is that peptides as small as approximately 70 amino acids are able to effectively compete with native IgE and displace the latter from the surface of mast cells. Considerable pharmaceutical research activity has focused upon strategies to block IgE binding to mast cells as a way to prevent the development of symptoms of allergic rhinitis and, indeed, all IgE-mediated allergic disorders.

IgE Receptors - Although a variety of immune and inflammatory cells express a low affinity receptor for IgE (FcϵRII, CD23), only mast cells and basophils express a high affinity (K_d 2-8 x 10^9) receptor for IgE. As described earlier, this receptor unexpectedly binds to the central portion of the constant region of heavy chain of IgE. Mast cells and basophils express 2-3 x 10^5 FcϵRI receptors on the cell surface. While engagement of as few as 1,000 can cause maximal exocytosis, 30-50 receptors can cause detectable exocytosis and may involve as few as 10-15 allergen molecules (depending upon the number of epitopes that are recognized by mast cell-associated IgE).

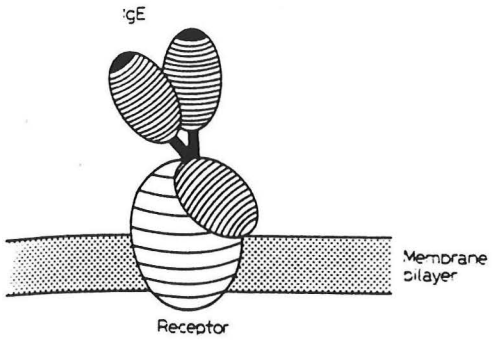

FIGURE 8

The rodent FcεRI has been extensively studied during the last decade and a great deal of progress has been made in its structural and functional characterization. A single receptor consists of one alpha subunit (45-50 kDa with a high carbohydrate content), one beta subunit (33 kDa) and two disulfide linked gamma subunits (8 kDa) as illustrated in Figure 9. From a functional perspective, the alpha subunit is principally directed toward the exterior of the cell and is exclusively responsible for binding to IgE. A soluble fragment of α can bind to IgE with high affinity and may become a useful agent in immunomodulation. Genetic analysis indicates the possible existence of alternative splicing

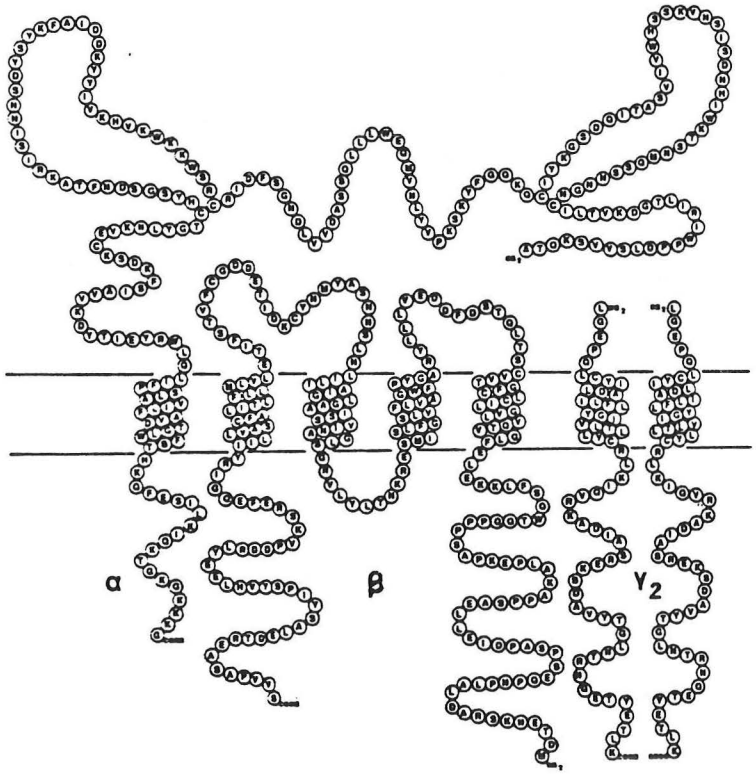

FIGURE 9

such that cells may potentially secrete a soluble form of α. Significant efforts have yielded substantial progress on the identification of the portions of the α subunit that provide specificity and high affinity to the binding of IgE. This effort has the possibility of generating new approaches to interfering with the interaction of antigen-specific IgE with its receptor as a mode of treating allergic disorders.

Although the function of the β subunit of the receptor is not well understood, the τ subunits have striking sequence homology to the zeta subunit of CD3 complex on T cells. That they have high structural and functional homology is indicated by the ability of coexpression experiments in oocytes (with the rat α and β subunit mRNA) that indicate that the human zeta chain can substitute for the rat τ subunit of FcϵRI in permitting surface expression of a receptor able to bind IgE with high affinity and is physically associated with the rat α and β subunits. Complex recent experiments involving chimeric constructs involving portions of alpha, gamma and the IL-2 receptor indicate that simple assignments of signal transduction properties to τ, however are somewhat premature inasmuch as constructs lacking τ can initiate a subset of second messenger pathways that are initiated by crosslinking the native FcϵRI.

Cell activation through FcϵRI - A common theme in antigenically specific cell activation in the immune system is the need to physically approximate relevant receptors (frequently referred to as "ligation" or "co-ligation"). A maximal exocytotic response can be seen with engagement of as little as 0.5 % of the 2-3 x 10^5 FcϵRI on the surface of a cell. The necessity of bringing two IgE bearing FcϵRI into close physical proximity in order to initiate antigen-dependent cell activation raises several important and clinically relevant concepts. First, in order to develop allergic sensitivity to a protein or glycoprotein, an individual must develop an IgE immune response to either: 1) one epitope of a homodimeric molecule or 2) two epitopes on a monomeric molecule in order to provide the opportunity of bringing two different IgE-bearing FcϵRI together by a single protein antigen. Second, the necessity to bring receptors into physical approximation indicates that the mechanism by which signals are generated will be different from those employed by receptors that simply respond to ligand binding. Thus, although it may be difficult to develop such reagents, the uniqueness of this receptor and limitation of this type of activation to cells of the immune system provides specificity so that effective pharmacologic interruption of IgE mediated mast cell activation may well not incur adverse effects in other effector systems. A common misconception is that the IgE that binds to the FcϵRI of a single mast cell is monoclonal. To the contrary, since IgE is synthesized at a distance and reaches the mast cell by the circulation, each mast cell will have a polyclonal population of IgE antibodies on its cell surface, rendering it capable of responding to a large number of different antigens to which it might come into contact.

Biochemical Mechanisms of Mast Cell Activation

A great deal of information has come to light in the last 10 years regarding the biochemistry of mast cell secretion. Although a detailed description of signal transduction

is beyond the scope of the current review, several observations are worth mentioning.

A Serine "Esterase" is Critical to Mast Cell Activation - Early studies in the 1960's suggested that activation of a membrane-associated enzyme with a catalytic serine in its active site was a critical early component of mast cell activation (shown by the ability of DFP to inhibit exocytosis if and only if it is present at the time cells are stimulated). The presence of nucleophilic serine residues has also been demonstrated in the active sites of a variety of hydrolytic enzymes outside the protease family suggesting that the target of DFP may catalyze cleavage of substrates other than peptide bonds of proteins.

The Role of G-Proteins in Fcϵ-RI Dependent Mast Cell Activation is Uncertain - Although recent work has shown that phosphoinositide hydrolysis in Fcϵ-RI stimulated RBL is inhibited by pertussis toxin, there is little data in intact cells suggesting a role for classic G-proteins in regulating FcϵRI initiated mast cell activation, although they do appear critically important in stimulation that does not involve FcϵRI.

cAMP and PKA - Participants with Uncertain Roles - Adenylyl cyclase was suggested to play a role in mast cell signal transduction inasmuch as antigen induced FcϵRI stimulation caused a dramatic, rapid and transient rise in the steady state levels of intracellular cAMP in mast cells and basophils. Thorough studies suggest that: 1) pharmacologically induced increases of cAMP may inhibit FcϵRI mediated exocytosis and 2) the effect of cAMP may be different for different parts of the cell.

Cytosolic Ca^{2+}: An Important Driving Force For Exocytosis - In studies using Ca^{2+} sensitive fluorescent probes, the concentration of cytosolic Ca^{2+} has been shown to increase during FcϵRI stimulation from 0.1 uM to 0.5-1.0 uM within 3 minutes after receptor crosslinking. In addition to the release of Ca^{2+} from intracellular stores (probably regulated by IP_3), an influx of extracellular Ca^{2+} is also associated with receptor-mediated activation. It has become increasingly evident that the roles of intracellular Ca^{2+} mobilization versus the influx of extracellular Ca^{2+} differ depending on the mast cell phenotype and species.

Phosphoinositide Metabolism: Two Second Messengers, but an Uncertain Role - Early studies in the mast cell demonstrated that all secretory agonists initiated rapid increases in phosphatidic acid (PA) and PI labeling by ^{32}Pi -- a reflection of the activation of the *PI cycle*. These changes were coincident with the onset of exocytosis and modified in parallel by physical conditions or pharmacologic agents that altered FcϵRI dependent exocytosis. The requirement for PI hydrolysis in mast cell exocytosis initiated by FcϵRI has been questioned since several agents that reduce PI-PLC failed to block Fcϵ-RI induced histamine release. The apparent importance of Ca^{+2} in exocytosis, however, makes it difficult to dismiss PI-PLC mediated liberation of IP_3 as being of little consequence.

Protein Kinase C: An Evolving Role - FcϵRI stimulation results in a rapid increase in both membrane associated and total PKC activity. Antagonists with preferential activity toward PKC reduce FcϵRI dependent exocytosis. Dampening enthusiasm for a central role

for PKC in regulating mast cell activation, however, are experiments that demonstrate that activating PKC by the addition of phorbol esters (PMA) cause little or no exocytosis. It seems likely that PKC may be an important, but not sufficient component of FcεRI dependent mast cell activation.

Phosphatidylcholine (PC) Hydrolysis by Phospholipase D: An Emerging Second Messenger Pathway - Increasing attention has focused on metabolism of PC since it has the potential to generate several second messengers [diacylglycerol (DAG) and PA] and/or requisite substrates (lyso-PAF and arachidonic acid) for the synthesis of newly formed lipid mediators, PAF and eicosanoids. FcεRI activation of ^{32}Pi prelabeled mast cells leads to rapid and sustained increases in PC labeling suggesting that at least some of DAG is metabolized to PC in a "PC cycle". Our own studies have shown that most of the DAG accumulating after Fcε-RI stimulation could not be derived from PI, but instead is formed from PC -- a finding suggesting that FcεRI-dependent PC hydrolysis was more important that PI hydrolysis in Fcε-RI dependent DAG accumulation. Whether phospholipase D or phospholipase C is of greater importance in the FcεRI initiated production of DAG from PC is the subject of ongoing studies in a variety of laboratories.

Phospholipase A_2 Activation: A Role in both Lipid Mediator Biosynthesis and Signal Transduction - The release of arachidonic acid (AA) from cellular phospholipids probably principally involves activation of PLA_2 although the ability of the mast cell to liberate AA from DAG has also been shown. The hydrolysis of 1,alkyl-2,acyl-PC by PLA_2 is also of interest inasmuch as it also generates the PAF precursor 1,alkyl-2,lyso-PC (lyso-PAF). In contrast to connective tissue mast cells which generate largely PGD_2 and little PAF, the mucosal mast cells synthesize predominately LTC_4 and PAF. Recent evidence suggests that PLA_2 mediated hydrolysis of phospholipids other than PC also may play a potentially important role in exocytosis.

Adenosine Facilitates Mast Cell Activation - Mast cells have surface adenosine receptors that, when stimulated, potentiate preformed mediator exocytosis from cells stimulated by FcεRI crosslinking. Although adenosine increases cAMP concentrations, the fluctuations in cAMP metabolism do not correlate well with mediator release suggesting that it acts through a mechanism other than PKA.

Tyrosine Kinase Activation - Recent studies demonstrate that tyrosine kinase activity is increased as the result of FcεRI stimulation and encourage a systematic assessment of both the role of this tyrosine phosphorylation in regulating mast cell activation and the presence of tyrosine kinase activity associated with Fcε-RI.

Impact of mast cell mediators on nasal physiology

When mast cells are stimulated by antigen-induced crosslinking of mast cell IgE receptors to secrete or synthesize histamine, PGD_2, LTC_4, PAF, and kinins a number of physiologic consequences are initiated. Histamine and other inflammatory mediators cause by direct and indirect mechanisms nasal obstruction, rhinorrhea, nasal pruritus and sneezing

(*vide supra*). In addition to mast cells, eosinophils recruited into the nasal epithelium can synthesize relevant mediators such as LTC_4 and PAF. The cytotoxic effects of eosinophil derived mediators (major basic protein, eosinophil cationic protein, and toxic oxygen metabolites) are likely more important in asthma than they are in allergic rhinitis.

Evidence supporting the physiologic role of these agents in the induction of allergic rhinitis was until recently limited to the ability of investigators to show that nasal instillation of histamine was able to provoke the effects described above and that these effects were largely blocked in antigen challenge by pretreatment with topical H_1 antihistamines. During the 1970's attempts at quantitation of nasal allergic responses were limited to the analysis of the resistance to air flow imposed by the nose (nasal airway resistance), but this technique is unfortunately insensitive and varies from lab to lab and patient to patient for obvious anatomic reasons (McClean et al, 1976). The observation that mast cells contain histamine and are able in vitro to obtained from allergic individuals were able to form these mediators was shown (Kaliner et al., 1973). The role of mediators in allergen-induced nasal reactions has been further supported by a technique that permits introduction of antigen into the nose followed by saline lavage of the nasal secretions and mediator analysis of these fluids (Naclerio et al., 1983). Mast cell derived mediators and/or granule markers such as histamine, kinin, and TAME esterase activity and tryptase have been shown to increase as the result of relevant challenge of the nasal mucosa with pollen grains or pollen extracts in patients with appropriate antigen-specific IgE. Detection of Leukotriene C4 and D4 released into in nasal secretions has also been accomplished (Fitzharris et al., 1985). Biopsy of nasal mucosa after antigen challenge reveals that greater than 90% of mast cells appear degranulated vs less than 20% after a control challenge (Corrado et al., 1985).

Major Allergens in Allergic Rhinitis

Figure 10 shows that there are 4 major classes of aeroallergens that typically participate in IgE mediated respiratory disease. These materials are typically particles in the range of 5-40 microns in diameter; a size that will render them airborne a significant fraction of the time, but still able to be effectively deposited upon the nasal mucosa during normal breathing. Recent interesting and provocative studies demonstrate that not all

MAJOR AEROALLERGENS

Pollens

Mold Spores

House Dust

Animal Proteins

FIGURE 10

antigens are carried on pollen grains but maybe carried in microdroplets much smaller than pollen grains as a result of elution of protein and/or carbohydrate antigens by water droplets and subsequent aerosolization. Indeed some protein allergens may actually be "in solution" in humid air (Solomon, 1984a).

Pollens. Plants reproduce sexually by producing on male portions of the plant pollen that is transferred to the female reproductive element by one of two major mechanisms. In the majority of what we consider "flowering" plants, pollination is mediated by insect transfer of pollen grains. For many trees, grasses and weeds, however, pollination is accomplished by the production of a large amount of pollen that is transferred by air currents. As a result, it is unusual to develop allergies to most flowering trees or plants because of the paucity of these pollens in the air. Pollen from plants that reproducing by wind borne pollination predominate and therefore cause the majority of pollen-induced allergic disease (Solomon, 1984 a&b). Pollens may travel several hundred miles.

Plant Pollen in Dallas

Major Aeroallergens		Pollination
Grasses	Bermuda	Spring-Fall
	Timothy	Spring-Fall
	Johnson	Spring-Fall
Weeds	Ragweed	Late Summer/Fall
	Marsh Elder	Late Summer/Fall
	Russian Thistle	Fall
Trees	Mt. Cedar	Winter/Spring
	Oak	Spring
	Elm	Spring
	Cottonwood	Spring
	Pecan	Spring

FIGURE 11

Because Dallas is in or near four different floristic zones, there is a diversity of pollens in the air for a very large fraction of the year. Figure 11 lists the major pollens in the Dallas/Ft. Worth area and the times that they are present. Most parts of the country endure pollen seasons of only 2-5 months duration, but it is typical for Dallas to have a pollen in the air for 9-11 months of the year. The only break is after the conclusion of the fall pollinating weeds with the coming of the first frost and before the emergence of mountain cedar pollen in with the first days of warm weather that typically break up our winter seasons. Most tree pollens emerge in the late winter/early spring. The grass season begins in late spring and extends through the fall with some reduction in the hot dry summer months. Most weeds pollinate beginning in august and continue until the first frost. It is, therefore, not surprising that many patients in the Dallas/Ft.

Worth metroplex with pollen-induced allergic rhinitis have only modest seasonal variation of their symptoms.

Molds - Mold spores can also be a significant cause of symptoms in this area. Mold spores are produced in greatest quantity during humid times of the year by several important genera including Alternaria, Hormodendrum, and Helminthsporum. Although mold spores are in the air all year long, the mold "count" is importantly affected by the presence of adequate moisture and permissive temperatures for growth and sporulation

House Dust - House dust is an important allergenic material present in even the most meticulously maintained households. It contains many poorly characterized antigens, but during the last 10 years it has been recognized that microscopic house dust mites (Dermatophagoides pteronissinus and D. farinae; 100-300 microns), are the source of the antigens responsible for most of house dust sensitivity in patients with allergic rhinitis and asthma. The house dust mite survives -- as it's name implies -- by consuming shed human skin or other epithelia such as feathers. The Der P1 antigen is a protease of 25 kDa that is present in very small micron fecal particles and is the dominant antigen in house dust allergy. This antigen collects in mattresses, pillows, carpeting, stuffed furniture, stuffed toys and heavy curtains. A popular misconception is that dust from dirt roads or construction produces IgE-mediated symptoms in house dust sensitive patients. Measures to reduce house dust mite derived antigen are dealt with in a subsequent section.

Animal Proteins - Pet danders are of considerable importance in allergic rhinitis. For the most part, major antigens are derived from animal saliva which is introduced into the fur by the animal's preening behavior. After drying, very small protein-containing particles are released into the atmosphere of the home. Fel D1 is the principal antigen for individuals with cat sensitivity and is present in enormous quantities in houses in which 1 or more cats reside even for only part of the day. This antigen causes very significant symptoms of perennial allergic rhinitis and/or asthma in atopic individuals. The extreme sensitivity of a significant subset of individuals having cat sensitivity predispose them to develop symptoms as the result of antigen present on the clothing of office coworkers and in homes in which the animal has been removed for weeks. Of considerable interest is the recent finding that weekly bathing of cat results in a greater than 90% reduction in the release of Fel D1 by such animals.

Although not classified as a pet, the exposure of atopic individuals to rodents (usually when working with laboratory animals) can result in very significant symptoms of allergic rhinitis and/or asthma after a period of working with these animals. With rodents, urinary proteins appear to be of principal importance in the pathogenesis of symptoms in exposed individuals who inhale these proteins.

Cockroach - Although the nature of antigens responsible for allergic rhinitis and asthma that are present as the result of cockroach infestation is the subject of considerable investigative effort, the concept that cockroach-derived allergens contribute to the perennial symptoms in a significant fraction of patients is taking greater root. Although successful

eradication is not easy and immunotherapy with insect extracts not widely utilized, recognition of cockroaches as a source of IgE-mediated disease will likely lead to improved management.

CLINICAL FEATURES OF ALLERGIC RHINITIS

Definition

A chronic or seasonally relapsing disorder that is characterized by the presence of nonpurulent rhinorrhea usually associated with some degree of nasal congestion, sneezing and nasal pruritus that is induced by exposure to aeroallergens that provoke a Type I (IgE-mediated) immune reaction in the nasal mucosa.

Historical Findings in Allergic Rhinitis

Important historical features in allergic rhinitis are listed in Figure 12 and include the production of nonpurulent clear nasal secretions that are usually watery, but not exclusively so. Allergic rhinitis may present at any age but is most commonly encountered in 10 to 40 year old individuals. It is uncommon for children under the age of 2 to have allergic rhinitis; perhaps the result of inadequate duration of exposure to aeroallergens necessary to mount a sufficient IgE immune response. Along these same lines, children with allergic rhinitis usually first show reactivities to perennial antigens (house dust, pet dander and mold) and later to pollens. Toddlers have increased dust exposure as a result of their proximity to carpet when they ambulate.

PATIENT HISTORY

- Clear vs purulent nasal secretion
- Seasonal changes
- Nasal pruritus
- Sneezing
- Presence of pets
- Associated disorders
  - symptoms of allergic conjunctivitis
  - sinus headache/infection
  - asthma
- ASA sensitivity/polyps
- Atopic family history
- Environmental history

FIGURE 12

Findings strongly suggesting an IgE mediated allergic cause for rhinitic symptoms include those attributable to histamine (nasal pruritus and frequent sneezing) and the association of symptoms consistent with allergic conjunctivitis (vascular engorgement, itching, burning and tearing) usually when nasal symptoms are maximal. Although not diagnostic, very few patients with allergic rhinitis of mild-moderate severity fail to have at least some improvement when H_1 antihistamines are used.

Allergic rhinitis may be seasonal or perennial although the latter often has seasonal exacerbations. The clinical history can give clues to the antigenic source of symptoms. For example, patients (working in an office setting) who are symptomatic primarily in the morning, improve during the day and become slowly worse in the evening are likely to be sensitive to an allergen present in the home such as house dust or a pet. Improvement at work correlates with the decreased presence of dust antigens in air as a result of more effective industrial air filtration and shorter pile carpeting. Alternatively, exacerbation during the weekend especially on outings suggest a pollen as the etiology. Certain aspects of the home environment are useful to obtain in the historical evaluation: 1) wall to wall carpeting, 2) pets, 3) humidifier use, 4) ceiling fan use, 5) daily exposures to animal or plant materials, 6) the type of mattress and pillow, 7) worsening of symptoms during vacuum cleaning, 8) occupational exposures, particularly to lab animals. Both allergic and nonallergic rhinitis may be exacerbated by exposure to irritants such as cigarette smoke, strong cooking odors or perfumes, although nonallergic perennial rhinitis (vasomotor rhinitis) shows greater nonspecific sensitivity. The presence of childhood asthma and/or atopic dermatitis is useful as a marker of the atopic diathesis.

Physical Findings in Allergic Rhinitis

Examining the nose, eyes, ears and sinuses is particularly important in patients with nasal obstruction and/or rhinorrhea. A summary of relevant physical findings frequently seen in patients with allergic rhinitis is presented in Figure 13. Nasal exam reveals enlarged edematous and frequently (approximately 50%) pale pink to pale blue nasal mucosa with increased clear nasal discharge. A very frequent misconception is that the mucosa in patients with allergic rhinitis is red. Erythema suggests infection or rhinitis

PHYSICAL FINDINGS

Facial	Nasal crease Allergic shiners Oral breathing ± Sinus tenderness
Nasal	Mucosal edema Mucosal pallor Obstruction Nasal discharge ± Polyps
Ocular	± Conjunctival vascularity ± Conjunctival edema
Otic	SOM
Pharyngeal	high arched palate/overbite postnasal drip

FIGURE 13

medicamentosa. Since the lateral width of the nasal passages is quite variable from patient to patient, the extent of nasal obstruction varies considerably. The nasal exam should describe the nasal mucosa with respect to: color, edema, the quantity and quality of nasal discharge, obstruction and the presence of polyps. Ocular exam for the presence of increased vascularity of the palpebral and/or bulbar conjunctiva is very useful. Transillumination of the sinus is of modest benefit even in the setting of suspected sinusitis, but any tenderness is important to note if historically relevant. Other physical findings that are variable but useful if present are the existence of a transverse cutaneous crease at the junction of the cartilaginous and bony part of the nose ("nasal crease" caused by frequent rubbing as in the "allergic salute"), the presence of significant overbite and high arched palate from oral airway breathing in childhood and the presence of discolored and thickened skin in the periorbital region ("allergic shiners"). The presence of tumors, foreign bodies or a deviated septum should, of course, also be noted. More thorough examination of the nose and nasopharynx is being performed routinely by some allergists and otorhinolaryngolists using small flexible fiberoptic rhinoscopes. This technique is particularly helpful for demonstrating polyps and purulent nasal secretions emanating from sinus ostia.

Laboratory Studies

Total IgE and eosinophils - These tests are rarely of value. Serum IgE levels in patients with perennial allergic rhinitis are not consistently elevated over those seen in patients with nonallergic rhinitis or normal individuals and therefore is not useful in the diagnosis of allergic rhinitis (Mygind et al., 1978). Circulating eosinophil counts are similarly of little value in the diagnosis of allergic rhinitis.

Nasal cytology - An important laboratory assessment that is frequently overlooked by nonspecialists is a simple Wright or Hansel stain of nasal secretions in a patient with active rhinorrhea. It can be performed in less than 5 minutes in the office and provides diagnostically useful information. Nasal secretions are obtained by either having the patient blow the nose into Saran Wrap or wax paper or by removing a small amount of material from the turbinate using a disposable Rhinoprobe^{R}. Staining requires approximately 1 minute and, after drying, microscopic evaluation can evaluate the presence of eosinophils. Untreated active allergic rhinitis usually demonstrates nasal eosinophilia although their absence on a single exam or in the setting of topical or systemic glucocorticoid therapy does not rule out allergy. Multiple noneosinophil containing nasal smears during periods of symptomatic rhinorrhea make the diagnosis of allergic rhinitis unlikely. Neutrophils and desquamated epithelial cells are typically seen in viral upper respiratory tract infection and sinusitis.

Antigen-specific IgE - Demonstrating antigen specific IgE in patients with suspected allergic rhinitis may be of important from diagnostic and therapeutic perspectives, but needn't be sought in most patients. The principal indications for assessing a patient with allergic rhinitis for the presence of antigen-specific IgE are: 1) in a patient with perennial symptoms, to confirm a diagnosis of perennial allergic rhinitis (vs. perennial nonallergic

rhinitis); 2) to evaluate whether a patient with allergic rhinitis is sensitive to antigens that can be the target for environmental control (principally house dust and animal proteins); and 3) for allergy specialists, to determine which antigens should be included in an extract to be used for immunotherapy in a patient with allergic rhinitis.

The presence of IgE antibodies can be determined by a variety of approaches. Skin testing involves the introduction of small amounts of allergen extracts into specific sites with the resultant development of wheal and flare responses to antigens to which a patient has antigen-specific IgE. It can be performed by epicutaneous (prick) and/or intradermal introduction of antigens. While the former has greater specificity and safety, it is less sensitive than the latter.

An increasing variety of in vitro tests also exist to detect antigen specific IgE in serum obtained from patients suspected of having allergic rhinitis (most having 4-5 letter acronyms rhyming with "past"). Although these in vitro tests can accurately detect antigen-specific IgE, their usefulness is limited by: 1) labs that are not reliable (lack of agreement between identical samples sent to a single lab or several labs); 2) cost ($500-1,000 typically for a routine battery); and 3) delay between drawing the tests and obtaining results. Skin testing is typically one quarter to one half of the cost of obtaining the same information using in vitro methods, more sensitive and performed rapidly. In vitro tests are useful in patients in the following settings: 1) generalized dermatitis; 2) dermographism; 3) when a life-threatening reaction to skin testing is a realistic consideration; 4) in children who are uncooperative; and 5) in patients necessarily taking pharmacologic agents with H_1 antihistamine properties (tricyclic antidepressants and some major tranquilizers).

A cost effective alternative for the primary care physician to determine whether a patient has sensitivity to dog, cat, housedust and few regionally determined antigens is the Quidel^R dipstick. This inexpensive office based test can be performed without any special equipment and generates useful information very rapidly.

Radiographic evaluation - Sinus radiographs and particularly sinus CT may be useful in patients with suspected chronic sinus disease. Ultrasound of the maxillary sinuses has not proven helpful in the diagnosis or management of sinusitis. The frequency of false negative plain radiographs in patients with sinusitis (approximately one third) has encourage greater reliance on CT examination of sinuses. Radiologists frequently will negotiate a substantially reduced charge for CT scans involving 5 mm cuts limited to the paranasal sinuses that generate only coronal reconstructions.

DIFFERENTIAL DIAGNOSIS

Nasal Obstruction

The differential diagnostic considerations of nasal obstruction are described in Figure 14. The more commonly occurring of these include pregnancy, septal abnormalities, polyps, increased adenoidal tissue and hypothyroidism. It is important to distinguish between the presence of absence of rhinorrhea in patients with obstruction. This distinction is not always straightforward, because, while anterior nasal discharge is obvious to patients, posterior nasal drainage or the "scratchy throat" or stale breath that frequently accompany it are often dismissed as modest or, more commonly, are assumed to be normal. Chronic post nasal drainage is not normal.

Differential Diagnosis of Nasal Obstruction

Structural	Deviated septum
	Choanal atresia
	Enlarged adenoids
	Foreign body
Vascular	Pregnancy
	Hypothyroidism
	Medications (antihypertensives, BCP, topical)
Other	Tumor (Benign + Malignant)
	Polyps
	Nasal Mastocytosis
	Infection

FIGURE 14

Rhinorrhea

The differential diagnosis of rhinorrhea is illustrated in Figure 15. Grossly purulent rhinorrhea takes place in a variety of upper respiratory tract infections complicated by bacterial overgrowth. Purulence is usually easily distinguished by history but almost always is apparent on gross or microscopic examination of the nasal secretions. The differential diagnosis of nonpurulent rhinorrhea can be subdivided into perennial and seasonal categories. Seasonal rhinorrhea is almost due to allergic rhinitis while perennial rhinorrhea may be either a result of altered basal neurovascular tone and/or exaggerated responsiveness to irritant stimulation (vasomotor rhinitis) or may be IgE mediated either as a result of multiple pollen sensitivities that span the year or to allergenic materials that have modest seasonal variation (house dust and animal proteins).

With perennial symptoms it is particularly important to perform cytologic evaluation of the nasal secretions because perennial rhinorrhea can be subdivided into three major disorders based largely upon the findings of the nasal smear. Secretions that repeatedly

do not contain eosinophils in the absence of positive skin tests results in the diagnosis of nonallergic perennial rhinitis (vasomotor rhinitis; a diagnosis made principally by excluding other etiologies). The presence of nasal eosinophils in substantial quantities suggests the diagnosis of perennial allergic rhinitis or perennial nonallergic rhinitis with eosinophilia (the so called NARE syndrome).

Differential Diagnosis of Rhinorrhea

Purulent	Bacterial rhinosinusitis
	Wegener's granulomatosis
	Kartagener's syndrome
	Cystic fibrosis
Nonpurulent	Acute
	CSF leak
	Irritant exposure
	Viral URI
	Seasonal = allergic rhinitis (SAR)
	Perennial
	With nasal eosinophilia
	Allergic rhinitis (PAR)
	Nonallergic rhinitis with eosinophilia (NARE)
	Without nasal eosinophilia = vasomotor rhinitis

FIGURE 15

The preceding discussion has emphasized clinical descriptions that are "classic". In reality, patients will often manifest combinations of allergic rhinitis, chronic sinusitis and/or vasomotor rhinitis with a primary impact of one. For example, a patient with perennial rhinitis (nonpurulent) may show modest nasal eosinophilia, a few significantly positive skin tests, high irritant sensitivity and a minimal response to a burst of prednisone. This hypothetical patient would be classified as primarily having vasomotor rhinitis with a modest allergic component and would be expected to show only a modest response to the use of H_1 antihistamines and/or topical nasal steroids.

CLINICAL MANAGEMENT OF ALLERGIC RHINITIS

OVERVIEW

Once the diagnosis of perennial or seasonal allergic rhinitis is made, therapy can be initiated using a variety of approaches. As with all IgE mediated allergic disorders, patient management hinges on three general therapeutic approaches: allergen avoidance, pharmacologic modulation and immunomodulation.

GENERAL MEASURES - Avoidance

While avoidance remains the optimum mode of therapy from the perspective of safety, it is not practical for the vast majority of patients. For pollen sensitivity, reduced exposure can be accomplished to a limited extent by using care to keep windows and doors closed and limiting time spent out of doors.

For perennial aeroallergens, however, patients are frequently able to markedly reduce their exposure. Although sometimes emotionally traumatic, removing pets from the home can make a profound difference in symptoms. Thorough cleaning of carpeting and upholstered furniture is required after the departure of the offending animal. Although less clinically successful, a more realistic goal is bathing the cat to reduce the antigen burden by >90%, particularly if coupled with a reduction in the time the pet spends in the home (particularly the bedroom).

A second perennial antigen that can be reduced considerably by environmental control is the house dust mite. Although not practical for nearly all patients, the house dust mite does not flourish at high altitudes making such sites as Davos, Switzerland havens of last resort for those with severe mite-induced asthma. Specific approaches that can be employed with all patients in their homes to diminish Der P1 content of bedding and carpeting are given in the Appendix. Acaracides are chemical agents with very little or no toxicity to animals or humans that have been developed that can kill the mites (Mitchell et al., 1985). Although quantitative measures of acaracide effectiveness in homes is somewhat controversial, the use of Acarosan^{R} appears fairly effective and safe, albeit somewhat expensive ($60-75/400 ft^2 every 3-6 months) in reducing Der P1 content of carpeting.

The value of air filtration devices (particularly room models) has been shown to be of little or no benefit to patients with allergic rhinitis. Factors that undermine their success apparently relate to: 1) a substantial rate of exchange of outdoor air in houses that are not "tight" in the case of pollen antigens; 2) the high rate of antigen generation by cats; and 3) the inability of these devices to rapidly handle huge increases in the content of antigen in the air when carpeting and/or bedding is disturbed by normal activity.

PHARMACOLOGIC MANAGEMENT

Overview

If allergen or irritant avoidance are either impractical or ineffective, pharmacologic therapy should be undertaken. This represents the cornerstone of management of the vast majority patients with allergic rhinitis. Figure 16 lists the agents that are able to improve the symptoms of this illness by reducing the release/synthesis of inflammatory mediators, by blocking the ability of inflammatory mediators to act upon target tissues and by reversing the end organ responses to relevant mediators.

Medications For Allergic Rhinitis

H_1 Antihistamines
Glucocorticoids (topical and systemic)
Cromolyn (topical)
Decongestants (topical and systemic)
Anticholinergics (topical)

FIGURE 16

Therapies that antagonize the release of mediators from mast cells include specific immunotherapy, topical cromolyn sodium, topical or systemic glucocorticoids and certain antihistamines. A second major class of medications block the formation of mediators of immediate hypersensitivity such as PGD_2 (by cyclooxygenase inhibitors), leukotrienes (lipoxygenase inhibitors) and histamine (histidine decarboxylase inhibitors). Agents that block the effect of released mediators by acting upon their target receptors involve H_1 antihistamines and leukotriene receptor antagonists. Decongestant medications (primarily alpha sympathomimetic agonists) represent an example of the ability of an agent to reverse the obstruction caused by vasodilation of capacitance beds and the edema associated with increased vascular permeability by causing vasoconstrictive reduction of flow to affected vessels.

Specific Agents

Antihistamines - A variety of classes of H_1 antihistamines are currently available. Substitution of side chain moieties can drastically alter the degree of antihistaminic effect as well as the type of side effects produced by each class of H_1 antihistamine. Given the high concentrations of histamine in areas of mast cell activation and the presence of a variety of other mediators causing vascular, glandular and/or reflex activity, it is not surprising that H_1 antihistamines are often unable to eliminate the symptoms of those suffering from moderate to severe allergic rhinitis.

Of greatest importance within this class of medications is the recent development of several antihistamines that have minimal capacity to cross the blood brain barrier (terfenadine, astemizole and cetirizine) and thus cause little or no sedation (Nair et al., 1985). Given the documented ability of older sedating medications to substantially impair

intellectual and driving performance, their use should be limited to bedtime or situations of extreme financial hardship. A recent concern regarding agents not limited by sedation (such as terfenadine and astemizole) is their association with increased Qt_c and ventricular arrhythmia (torsade de pointes) in situations in which excessive blood levels develop: 1) intentional overdose; 2) use by patients and/or physicians at doses exceeding those approved; and 3) use at appropriate doses in the setting of reduced hepatic metabolism particularly with macrolide antibiotics and ketoconazole. Patients must be warned of these drug interactions and accidental or purposeful overdoses with these agents mandate electrocardiographic monitoring and consideration of methods of accelerating clearance of depending on the clinical situation.

Many antihistamines such as doxepin, azelastine and astemizole have prolonged effects and can interfere with skin testing for 4-10 days or more depending on the agent (Atkins et al., 1985). For this reason, long acting agents should be used judiciously in patients who will or may need skin testing in the near future.

Cromolyn Sodium - Cromolyn sodium has been used for many years in the treatment of asthma (Pepys et al., 1974). Although this agent has been purported to "stabilize mast cell membranes" its mechanism of action is not well understood. Further, it has important effects on a variety of cells in addition to the mast cell. Nasal cromolyn (Nasalcrom) has been successfully used in both seasonal and perennial allergic rhinitis but its effectiveness seems to be somewhat less consistent than that of topical nasal steroids (Cohan et al., 1976) and its monthly cost is substantially greater. In the favor of this medication, however, is its safety for use in children and in pregnancy. A more powerful medication in this same class is Nedocromil (Tilade^R) is available in Europe and will likely become available in the US in the near future.

Topical Glucocorticoids - Topical glucocorticoid preparations are highly effective in reducing symptoms of seasonal allergic rhinitis and perennial allergic rhinitis (as well as having a positive impact upon the NARE syndrome and chronic nasal polyposis). Long term treatment studies reveal that chronic administration of topical nasal steroids for 5 to 10 years does not result in atrophy of nasal mucosa and is without substantial significant side effects (Norman, 1983). The dose necessary to cause significant reduction in adrenal corticosteroid formation is quite high (beclomethasone requires doses 3-6 fold greater than the maximum recommended dose; Harris et al., 1974). ACTH stimulation testing is normal in individuals treated with conventional doses of these medications. These medications cause a marked decrease in the presence of mast cells in the superficial nasal epithelium and a decrease in the release of mast cell derive mediators from patients challenged with antigen.

Several important practical issues are often overlooked by physicians prescribing this medication. First, and most importantly, this medication requires 4-7 days to achieve near maximal relief of symptoms. As a result, patients must be instructed to expect this delay and not discontinue this medication when symptoms seem only modestly altered after several days. Additionally, this medication should principally be used on a regular basis

to prevent symptoms with antihistamines used PRN to deal with break through symptoms. Second, the impact of this medication does not dissipate quickly and, as a result, patients who are seeking to reduce their dose (in the face of feeling well) should do so slowly in order to allow a realistic assessment of the impact of a dose reduction. Third, that these medications are not related to androgenic steroids should be emphasized to many patients who worry that all medications in the "steroid" class are illicit and/or dangerous. Fourth, the use of these medications in children is more controversial and should, in general, be reserved for specialists since data indicate that modest, but significant effects of inhaled glucocorticoids on growth rate (in children with asthma) are seen. Fifth, concerns over septal perforations are markedly attenuated by the use of aqueous preparations that avoid the repetitive drying and irritative effects of nasal MDIs that may cause ulcerations of the nasal septum and/or anterior portion of the inferior turbinate. Sixth, minor epistaxis is encountered with a small, but significant fraction of patients. In most, transient replacement of the topical glucocorticoid therapy in the affected nostril with nasal saline for several days results in resolution without its return. Some patients complain about the "runniness" and/or the smell of the aqueous suspensions of beclomethasone. Although there has been somewhat less experience with nasal triamcinolone (Nasacort^R), it appears to be highly effective in daily or BID dosing and very well tolerated. Finally, topical dexamethasone should no longer be used as the result of rapid substantial absorption and the resulting systemic effects.

Decongestants - Decongestants used to treat allergic rhinitis fall within the class of α adrenergic agonists that function by causing vasoconstriction of both resistance and capacitance vessels resulting in relief of obstructive symptoms. The most commonly used topically applied decongestant is 0.05% oxymetazoline (Afrin^R, Nostrilla^R, etc). Although these medications are extremely potent they have the unfortunate property of causing the development subsensitization during continuous use. Because subsensitization diminishes the relief obtained by patients, it is not uncommon for patients to enter into a cycle that results in its use at frequencies that often greatly exceed that which is recommended (as often as q 30 minutes). This "addiction" is termed rhinitis medicamentosa and can itself cause damage to the nasal mucosa. Excessive fear of developing this syndrome on the part of both patients and physicians coupled with relative ignorance on the part of the latter in the appropriate use of this agent has resulted in overlooking a very helpful modality of therapy in certain clinical situations. Figure 17 illustrates a personal view of situations in which topical decongestants can be helpful.

Although few careful studies exist, it is widely appreciated that topical or systemic glucocorticoids will prevent and/or reverse the subsensitization phenomenon that can complicate the use of α adrenergic agents such as oxymetazoline. For the therapy of those with rhinitis medicamentosa, a 5-7 day course of systemic glucocorticoids (prednisone 40 mg daily for adults) with discontinuation of the topical decongestant on day 2 is highly effective. Similarly, the regular use of topical nasal glucocorticoids at moderate doses appears to prevent subsensitization when oxymetazoline is used on a daily basis within recommended dose ranges.

Topical Decongestants - Potential Indications

Acute	Severe untreated allergic rhinitis
	Acute sinusitis
	Breakthrough obstruction with allergic rhinitis
	Prior to anticipated barotrauma
Chronic*	Obstruction > rhinorrhea in allergic rhinitis
	Chronic and recurrent sinusitis

* with topical glucocorticoids

FIGURE 17

Oral decongestants such as pseudoephedrine and phenylpropanolamine hydrochloride are also alpha sympathomimetic agents, but use of these agents is often limited because of the neuropsychiatric symptoms (tremor and CNS stimulation) that often accompany pharmacologically relevant doses. These agents are, of course, considerably less effective than topically applied decongestants and can induce or exacerbate hypertension if high doses are used. They are not associated with a significant subsensitization phenomenon, however. A large number of medications provide fixed combinations of pseudoephedrine and H_1 antihistamines.

Topical Anticholinergics - For some time ipratropium bromide (Atrovent^R) has been available in Europe and Canada for the treatment of refractory rhinitis and in the US for the treatment of chronic bronchitis. In the nose, this agent acts by blocking cholinergic stimulation of mucus hypersecretion and thus has a primary impact on rhinorrhea. Because the reflex-mediated portion of the rhinorrhea associated with allergic rhinitis is mediated by the release of acetylcholine by postganglionic parasympathetic neurons, it can be substantially attenuated by the administration of an topical anticholinergic such as ipratropium bromide. Thus, this type of medication can have a significant effect on this aspect of a patient's symptoms, but will provide virtually no relief for obstructive symptoms associated with allergic rhinitis. Thus, its use remains largely adjunctive to that of topical steroids and H_1 antihistamines as is discussed subsequently.

Perhaps the most useful aspect of ipratropium bromide lies not with its ability to improve allergic rhinitis but with its capacity to offer an effective approach to treating patients with vasomotor rhinitis, for which none of the medications described above and below are consistently effective (Borum et al., 1979 and Dolovich et al., 1985). In addition to its use in allergic and vasomotor rhinitis, double blind randomized trials in Europe and personal experience indicate that Atrovent can be a very useful therapy in treating the rhinorrhea associated with the common cold (Borum et al., 1981).

Several practical aspects of nasal use of ipratropium bromide are important. First, application of Atrovent for nasal symptoms requires reducing the diameter of the oral MDI to that appropriate for a nostril. This is accomplished by placing a baby bottle nipple over the MDI opening and cutting the nipple at its narrow end so that an orifice of

approximately 6 mm is created; comfortably entering the nostril. Second, typical dosage regimens to reduce rhinorrhea are 1-2 puffs in each nostril BID-TID PRN. Third, although this represents an "off-label" use of this medication, the lack of systemic absorption of this quaternary amine containing agent makes its use very safe. Many physicians feel that concerns related to its use in the setting of existing prostate disease and pregnancy are minimal. Fourth, while systemic adverse effects are virtually nil, patients may have to balance effective reduction of rhinorrhea with the development of dryness of the pharynx. Further, patients should take considerable caution in avoiding spraying this medication into the eyes since it is a potent anticholinergic agent.

Systemic glucocorticoids - Systemic glucocorticoids are extremely effective in reversing allergic rhinitis; usually after 24-48 hours. The impact of glucocorticoids is impressive, although the mechanism by which this effect is mediated is less certain. Although high dose steroid treatment has little or no effect on the immediate wheal and flare response of skin testing, in vitro rodent mast cell mediator release can be reduced by pretreatment with glucocorticoids (Marquardt and Wasserman, 1983). Human nasal challenge studies demonstrate reduced release of mast cell-derived mediators as well. A reduction in lipid mediator formation by the inhibition of phospholipase(s) through the steroid-mediated induction of the synthesis of lipomodulin (Macrocortin) (Blackwell et al., 1980 and Hirata et al., 1981) has been proposed, but recent evidence makes it extremely unlikely that the hypothesis has relevance in vivo.

Indications for using systemic glucocorticoids in allergic rhinitis is a subject of some debate. Virtually all responsible physicians agree that the use of injections of long acting glucocorticoids and chronic use (more than one week) of short acting oral medications is inappropriate. Similarly, these medications should not be used in anyone with a relative contraindication to them since allergic rhinitis is not a life threatening illness. Appropriate use in young and otherwise healthy adults is defined somewhat differently for each physician.

Systemic glucocorticoids can be particularly useful in initiating therapy in patients with moderate to severe allergic rhinitis since nasal obstruction will markedly impair delivery of topical steroids and/or cromolyn to the nasal mucosa. In these patients the physician is left either with using topical decongestant medications or systemic steroids or with accepting a very slow response to topical steroids (which often results in poor compliance). In the patient who has never used topical decongestants, their use may represent an introduction to a medication that may become used in an abusive fashion. When systemic glucocorticoids are used in an inductive fashion in severe allergic rhinitis, a typical course would involve the use of prednisone (40 mg/day) for 3-5 days with the concommitant introduction of topical glucocorticoids. Dramatic improvement is usually seen within 24-36 hours. Some situations in which allergists choose to use systemic glucocorticoids are listed in Figure 18.

In the patient with rhinitis medicamentosa, systemic glucocorticoid treatment (30-40 mg of prednisone) for 5-7 days permits the rapid withdrawal of nasal decongestants (on

day 2) without the occurrence of rebound nasal obstruction. The mechanism presumably represents reestablishment of the normal functioning of the α adrenergic receptor.

Systemic Glucocorticoid Therapy in Allergic Rhinitis

Diagnostic trial (to establish the diagnosis of AR)
Initiation of therapy in severe AR (with topical steroids or cromolyn)
Control of severe symptoms (rarely)
Rhinitis medicamentosa
Enhancement of therapy of complicating sinusitis

FIGURE 18

In patients where the allergic basis of rhinitis is uncertain, treatment with systemic glucocorticoids may be of diagnostic value because nearly all patients with allergic rhinitis or the NARES syndrome have marked improvement in their symptoms. Patients with perennial non-allergic rhinitis (vasomotor rhinitis) tend not to improve. When used in this setting, it is important to use systemic glucocorticoids only for 3-5 days and to ask how quickly an improvement (if any) takes place and when symptoms return. Substantive improvement of symptoms within 2-6 hours of the initiation of therapy indicates a placebo response.

Novel Drug Therapies

Although substantial controversy exists over its scientific basis, a five amino acid peptide that represents the amino terminal five residues of the C_{H1} region of the ϵ chain of IgE is in clinical trials. Modest benefit in double blind, placebo controlled trials has been seen. The role this medication might play in therapy of allergic rhinitis is uncertain.

A variety of medications that antagonize the synthesis of leukotrienes (lipoxygenase inhibitors) or their block their interaction with target receptors (leukotriene receptor antagonists) hold the possibility of efficacy in allergic rhinitis by blunting the vascular and glandular effects of LTC_4 and LTD_4. Thus far trials have shown modest efficacy; a finding that is not unexpected given the panoply of mediators generated by mast cells and recruited eosinophils and the ability of this class of agents to antagonize only one class of them.

In addition to these agents that act by mechanisms independent of those discussed above, a variety of new agents within existing classes are being developed and include: topical glucocorticoids (budesonide, fluticasone); nonsedating antihistamines (cetirizine); cromolyn (nedocromil); topical anticholinergics (oxytropium).

IMMUNOTHERAPY

Overview

The use of extracts of aeroallergens for the therapy of allergic rhinitis is one of the oldest of modern immunotherapeutic approaches; first reported by Noon in 1911. Although a number of improvements have been made during the ensuing 80 years, it remains only modestly different today than it was 30-50 years ago. Because this form of therapy largely remains the purview of allergy subspecialists (or should, at least), only general concepts will be discussed in the current context.

General and Practical Aspects

Although a number of variations exist, most authorities in this field agree that the most successful approach to allergen immunotherapy (IT; or immune "desensitization") involves the high dose administration of aqueous extracts of aeroallergens to which an individual has both IgE antibody and a clinical reaction. The simple existence of allergen-specific IgE (detected by skin testing or *in vitro* methods) is not alone sufficient justification for treating this "sensitivity" if a patient's history does not indicate that relevant seasonal or chronic exposure fails to cause symptoms. Similarly, the residence of a person in an area where many patients have a certain IgE aeroallergen sensitivity should not motivate treatment with an allergen in the absence of documented IgE sensitivity (which has been anecdotally described to cause sensitivity that does not respond to IT). For these reasons, coupled with the occasional severe systemic reaction, **allergen immunotherapy should be initiated by a allergy subspecialist and performed in a supervised medical setting.** Typically, a mixture of appropriate extracts is made, diluted by serial ten fold dilutions and 0.05 cc of 1:1,000 or 1:10,000 dilution of the concentrated vial administered SQ as the first dose. Depending on the clinical situation, the preference of the patient and that of the physician, doses are increased by 1.5-2 fold each time and given every 3-7 days. The development of a substantial wheal and flare reaction during the 15-30 minutes after administration usually motivates a slower pace. Although special "rush" immunotherapy protocols exist for unusual situation, the achievement of a maintenance dose (typically 0.5 cc of the most concentrated mixture of allergen extracts) usually takes 3-6 months to achieve. Once maintenance doses are achieved, the dosing interval is gradually increased to 4-6 weeks.

Safety and Efficacy

Efficacy in 80-90% of correctly diagnosed patients has been established in double blind placebo controlled trials with many different antigens. Most patients note improvement within 3-6 months, but one year is needed in some. Once this maintenance therapy has been achieved, it is maintained for varying periods of time. No controlled data are available, but widespread anecdotal experience indicates that after approximately 3 years of maintenance immunotherapy with high dose extracts, approximately half to two thirds of patients who discontinue therapy will retain a durable remission for these antigens. In the rest, reaffliction with significant symptoms typically requires a number of

years. The ability of allergen immunotherapy to cause a decreased need or elimination of regular medication use makes this approach to therapy is cost effective in patients who have two season rhinitis and take two medications regularly; particularly if immunotherapy is ultimately discontinued.

A number of issues pertaining to safety of immunotherapy are important. First, although not predictable in any given patient, immunotherapy causes systemic reactions ranging from mild urticaria to full blown anaphylaxis. The frequency of any systemic reaction is approximately 1:1,000 injections. The frequency of reactions that might cause mortality if untreated is approximately 10 fold less common. Although severe anaphylaxis is infrequently seen (even by allergy subspecialist; perhaps 1:100,000 injections), the ability of a physician to provide immediate and full therapy (readily available epinephrine, IV materials, laryngoscope and ET tubes, knowledge of emergent cricothyroidotomy, etc.) is imperative prior to embarking upon this form of therapy. Most severe reaction take place as the result of medication errors or inadvertent IV administration. Reports of the rare cases of fatal reactions to immunotherapy often involve self administration, failure to wait in a physician's office for 20-30 minutes after an injection or inadequate care by the physician.

Inadequate or inappropriate immunotherapy

It is a common and appropriate practice for allergy specialists to provide reagents and guidance to primary physicians who administer allergen immunotherapy to their patients. Unfortunately, a variety of nonspecialists without substantive training in this discipline treat patients without appropriate diagnoses with homeopathic levels or "provocation/neutralization" approaches that have been shown by careful studies to be devoid of effectiveness. Indeed, it is estimated by some that these practices represent one of the five most common forms of health fraud or waste today; incurring many millions of dollars of unnecessary costs. Although not always true, general indications that a given patient is receiving or has not received an effective course of immunotherapy would include are: 1) administration of extracts at maintenance levels that are without color (except for isolated therapy for house dust mite or cat) unless prevented from doing so by local reactions; 2) the absence of delayed local reactions during the entire course of therapy; and 3) administration during the last 5 years of extracts at home.

Scientific Basis

The mechanism(s) by which allergen immunotherapy provide relief to patients with allergic rhinitis are poorly understood, despite considerable effort on the part of a number of outstanding investigator. Although for years it was assumed that the development of antigen-specific IgG antibodies acted to block access of allergen proteins from gaining access to IgE bearing mast cells, considerable doubt has been cast upon this hypothesis. Although the immediate wheal and flare response to skin testing for an antigen typically changes little if at all as the result of allergen immunotherapy, a late cellular late phase reaction (4-12 hours later) is found to be markedly attenuated. In contrast, allergen

immunotherapy diminishes the acute nasal responses to allergen administration both in natural and laboratory settings has been shown. The explanation for these site differences in IgE dependent reactions has remained elusive. Offered by some groups is that allergen immunotherapy reduces the allergen-dependent generation of ubiquitous and heterogenous molecules termed *histamine releasing factors* (due to their ability to cause basophil or mast cell exocytosis). Further, the ability of chronic administration of antigen to change the affinity of IgE is felt by some to be of importance.

Future Potential Approaches to the Treatment of Allergic Rhinitis

Figure 19 lists approaches that are currently under active consideration and/or trial. The ability to abrogate future IgE responses in rodent models by the neonatal administration of anti-IgE antibody is of considerable interest for individuals with parents who carry the atopic tendency. Recent recognition of an epitope of IgE that is expressed on the surface of B cells, but not present in secreted IgE raises the possibility that IgE produceing B cells could be selectively destroyed by appropriate immunotoxins. Attenuation of existing IgE responses by using IFN-gamma (as can be accomplished in a murine system) has not proven of clinical efficacy in human disease; probably the result of inability to tolerate the doses of IFN-gamma that would be necessary. As described earlier, fragments of IgE that span the C_{H2} and C_{H3} regions of the epsilon heavy chain as small as 68-76 amino acids can effectively block native IgE binding the FcϵRI. A tremendous growth in the studies examining the potential applications of soluble recombinant human interleukin/cytokine receptors has taken place in the last few years. Coupled with efforts to generate soluble blocking agents of adhesion molecules, it seems quite possible, that quite selective antagonism of leukocyte emigration into sites of IgE-initiated allergic inflammation might be possible.

Potential Future Therapies

* Prevent new IgE immune responses
* Attenuate existing IgE immune responses
* Destroy IgE producing B cells
* Block IgE binding to FcϵRI
* Inhibit late phase reactions with sIL-R and adhesion molecules
* Antagonizing signal transduction involving FcϵRI

FIGURE 19

Management Strategies in Allergic Rhinitis

The choice of an approach to managing patients with allergic rhinitis depends upon a number of factors: 1) age; 2) current or anticipated pregnancy; 3) severity of symptoms; 4) duration of symptoms during the year; 5) financial resources/insurance coverage; 6) availability of subspecialty care (allergen immunotherapy); and 7) concern over the chronic

use of medications. Figures 20-22 illustrate a personal view of the management by nonspecialists of patients subdivided by severity.

Approach to Mild Allergic Rhinitis

* Testing for pet and mite IgE ---> avoidance
* PRN nonsedating H_1 antihistamines
* Subspecialty referral not necessary

FIGURE 20

Approach to Moderate Allergic Rhinitis

* Testing for pet and mite IgE ---> avoidance
* Regular use of topical glucocorticoids
* PRN nonsedating H_1 antihistamines
* Subspecialty referral for:
  - Inadequate response to therapy
  - > 6 month allergy symptoms/year (for IT)
  - Concern with chronic Rx use (for IT)
  - Anticipated pregnancy (in $\geq$ 6 months)

FIGURE 21

Approach to Severe Allergic Rhinitis

* Acute use of topical decongestants or systemic glucocorticoids
* High dose regular use of topical glucocorticoids
* Regular or PRN use of nonsedating H_1 antihistamine
* Additional agents depending on clincal situation
  - Cromolyn
  - Nasal ipratropium bromide
  - Topical decongestant
* Subspecialty referral

FIGURE 22

Pregnancy - Pregnancy represents a common challenge to both the primary physician and allergy subspecialist. Considerable controversy exists about the appropriate management of these patients given the paucity of studies to specifically address safety

issues of a variety of the medications typically used in the management of adults with allergic rhinitis. Additionally complicating the management of these patients is that the impact of hormonal changes on the nasal vasculature results in substantially increased obstruction in a large fraction of patients. The frequency of inadvertent use of terfenadine early in the first trimester of pregnancy and the lack of reported cases of adverse impact upon the outcome of the pregnancy support the concept that its use is likely to be safe, but no specific data exist to generate confidence in this view. The ability of alkylamines (notably brompheniramine) to cause abnormalities in laboratory animals strongly discourages its use and tripelennamine is typically recommended. The lack of significant systemic absorption of cromolyn makes it a first line medication in this setting. Unfortunately, in patients with moderate or severe disease, it is rarely able to provide adequate relief. Although no specific data exists with regard to the use of ipratropium bromide, its similar lack of absorption encourages the view that it can be used with considerable safety to deal with symptoms of rhinorrhea. A great deal of controversy exists with regard to the use of topical nasal steroids in the setting of pregnancy. The successful outcomes of pregnancies in which this class of medications is used to manage asthma encourage considerable confidence in its use in allergic rhinitis. Its classification as a Category C medication, however, discourages many physicians, but this categorization relates to the demonstrated ability of these medications to cause fetal abnormalities at large doses when administered parenterally. The very modest absorption of topical glucocorticoids coupled with substantial clinical efficacy have led a number of allergy subspecialists to use these agents during pregnancy, albeit judiciously. Dealing with congestive symptoms with systemic α adrenergic agents has been felt to be reasonably safe, despite their ability to cause vasoconstriction. As long as caution is used to avoid rhinitis medicamentosa, topical oxymetazoline represents a very helpful therapeutic tool for obstructive symptoms.

Immunotherapy is a very useful modality for treating pregnant patients with allergic rhinitis. Systemic reactions involving hypotension occur, albeit rarely, particularly during the period of allergen immunotherapy when doses are increasing. As a result, most allergists will not recommend the initiation of immunotherapy during pregnancy, but feel confident in continuing a modestely reduced maintenance dose in the pregnant patient.

Approaches to Allergic Rhinitis in Pregnancy

* Antecedent testing and IT ---> maintenance IT
* Topical cromolyn
* PRN or judicious regular oxymetazoline (obstruction)
* Topical ipratropium bromide (rhinorrhea)
* Judicious topical nasal glucocorticoids
* PRN tripelennamine

FIGURE 23

Thus, if a woman anticipates near term pregnancy, but not within the next 3-6 months,

allergy subspecialists can usually achieve a maintenance dose and clinical improvement within this time frame. Inasmuch as this modality of therapy can markedly reduce or eliminate the need for medications for allergic rhinitis, this probably represents the safest approach to treating allergic rhinitis in pregnancy.

Allergic Rhinitis in Children - Although a subject that is not typically a concern of internists, a brief discussion of the management of children with this illness is worthwhile in this context. First, a very important aspect of the assessment of children with allergic rhinitis is that parents and physicians frequently underestimate the severity of this illness. For many children, they have been enduring these symptoms for as long as they can remember and, as a result, tend not to complain to the same degree as an adult would with identical symptoms. This is particularly an issue when children are examined at a time when their symptoms are submaximal as the result of seasonal variations (when they are seen principally during routine health examinations) or pharmacologic suppression by administration by parents of OTC medications or even their own prescription medications (given the genetic transmission of the atopic diathesis).

For children under the age of approximately 10, most subspecialists seek to refrain from allergen immunotherapy, although testing for allergens that can be reduced by environmental measures (house dust mite, pet and certain mold antigens) is often useful.

While most of the newer medications for adults have not been approved for use in younger children, a number of them are routinely used with success. Because of safety concerns, topical cromolyn is used more commonly than topical nasal steroids in children. Data obtained in children regularly using topical glucocorticoid therapy for asthma indicate minimal, but significantly reduced growth compared to children treated with theophylline in a double blind comparative study. However, failure of cromolyn and appropriate antihistamine therapy should not prevent the judicious use of topical nasal glucocorticoids in children; particularly in light of the frequent development of facial abnormalities in children with chronic oral breathing due to nasal obstruction. Recent concerns over the rare association of ventricular arrhythmias when excessive doses of nonsedating antihistamines are used in healthy adults motivate the careful dosing of these agents in small children. Although not a safety issue, the psychomotor agitation associated with the use of systemic decongestants and sedation caused by sedating H_1 antihistamines can be troublesome in children; particulary pertaining to school performance.

An important aspect of the management of children is care to avoid overlooking the potential existence of chronic sinusitis in children with allergic rhinitis. The existence of headache or purulent anterior or posterior nasal discharge should alert the physician to the potential existence of chronic sinusitis which accompanies the initial diagnosis of allergic rhinitis is children in as many as half of cases. While controversy exists over the role of empiric antibiotic therapy, radiographic assessment and delaying antibiotic therapy until the impact of anti-allergic therapy can be assessed in this setting, this frequent problem should not be missed.

Allergic Rhinitis in Children

* Testing for mite/pet sensitivity ---> avoidance
* PRN H_1 antihistamines $\pm$ decongestants
* Topical cromolyn (Nasalcrom or Opticrom)
* Assessment of chronic sinusitis
* Judicious regular use of topical glucocorticoids

FIGURE 24

ALLERGIC CONJUNCTIVITIS

Frequently complicating allergic rhinitis is allergic conjunctivitis. Usually the symptoms of this associated illness are less severe, than nasal symptoms but at times of severe nasal disease, ocular manifestations can become extremely uncomfortable (tearing, burning, itching and edema of conjunctiva). The additional presence of allergic conjunctivitis only modestly alters the management of allergic rhinitis. First, symptoms can be conservatively managed simply often by the frequent use of liquid tears to remove offending antigens. There are virtually no adverse effects of this approach. Second, while topical steroids have little or no adverse effects when used intranasally, the potentially severe complications associated with their intraocular use mandates that these medications be used exclusively by ophthalmologists. Unfortunately, an ophthalmic preparation of cromolyn (Opticrom^R) has been removed from the market by the FDA as the result of a production deficiency. Because Opticrom has not returned to the market quickly, the requests by a number of physicians have motivated a limited number of pharmacists to prepare 4% cromolyn solutions in ophthalmic solutions. Finally, in patients with allergic conjunctivitis many allergists have a lower threshold for the regular use of H_1 antihistamines because of their ability to diminish the symptoms of allergic conjunctivitis. Topical H_1 antagonists are available (pheniramine), but always in combination with vasoconstricting substances. Because of the potential development of subsensitization to the α adrenergic components of these preparations (Opcon^R and Naphcon A^R), their use should be occasional when burning or itching becomes severe. A hiatus in therapy using these topical antihistamine/decongestant preparations (one day out of every 3-4 day) markedly reduces the likelihood of the development of subsensitization.

REFERENCES

Historical Aspects of Allergic Rhinitis

Blackley, C.H. 1873. Experimental researches on the causes and nature of catarrhous aetinus. Balliere, Tindal and Cox, London.

Bostock, J. 1819. Case of a periodical affection of the eyes and chest. Med. Chir. Trans. 19: 161.

Bovet, D. and A.M. Staub. 1937. Action protectrice des ethers phenoleques au cours do 1'intoxication histaminique. Compt. Rend. Soc. Biol. 124: 547.

Dale, H.H. and P.P. Laidlaw. 1911. The physiologic action of beta-immazolylethylamine. J. Physiol. 41: 318.

Ehrlich, P. 1878. Beitrage zur theorie und praxis der histologischen farbung. Thesis. University of Leipzig.

Ishizaka, K. and T. Ishizaka. 1967. Identification of E antibodies as a carrier of reaginic activity. J. Immunology 99: 1187.

Jorpes, E., H. Holmgren and O. Wilander. 1937. Ueber das vorkommen von heparin in den gefasswanden und in den augen. Ztschr. Mikros. Anat. Forschg. 42: 279.

Noon, L. 1911. Prophylactic inoculation against hay fever. Lancet 1: 1572.

Prausnitz, C. and H. Kustner. 1921. Studien uber uberempfindlichkeit. Centralbl. f. Backteriol. 1 Abt. Orig. cp. 6: 160.

Riley, J.F. 1953. Histamine in tissue mast cells. Science 118: 332.

Von Pirquet, C. 1906. Allergie. Munch. Med. Wochenschr. 53: 1457.

West, G.B. 1955. Histamine in most cell granules. J. Pharm. Pharmacol. 7:80.

Epidemiology

Ericsson, C.H., M. Svartengren, B. Mossberg, N.Pederson and P. Camner. 1991. Bronchial reactivity and allergy-promoting factors in monozygotic twins discrodant for allergic rhinits. Annals of Allergy. 67(1): 53-9.

Gergen, P.J. and P.C. Turkeltaub. 1991. The association of allergen skin test reactivity and respiratory disease among whites in the US population. Data from the Second National Health and Nutrition Examination Survey. Arch. Int. Med. 151(3): 487-92.

Hagy, G.W. and G.A. Settipan. 1971. Prognosis of positive allergy skin tests in an asymptomatic population. J. Allergy and Clin. Immunol. 48: 200.

Hess, A., and D. Lyon. 1985. Allergic rhinitis - A major study of the habits and attitudes of consumers. J. Allergy Clin. Immunol. 75: 381(A) (abst.)

Smith, J.M. 1984. The epidemiology of allergic rhinitis. In: Rhinitis. Ed. G.A. Settipane. The New England and Regional Allergy Proceedings. Providence, pp. 86-91.

Turkeltaub, P.C. and P.J. Gergen. 1991. Prevalence of upper and lower respiratory conditions in the US population by social and environmental factors: data from the second National Health and Nutrition Examination Survey, 1976 to 1980. Annals of Allergy. 67(2 Pt1): 147-54.

Basic Aspects of Nasal Function

Andersen, I., G. Lundqvist, P.L. Jensen, and D.F. Proctor. 1974. Human response to controlled levels of sulfur dioxide. Arch. Environ. Health 28:31.

Mygind, N. and L. Malm. 1982. Pathophysiology and management of allergic and non-allergic rhinitis. In: The Otolaryngology Loose Leaf Series. Ed. G.M. English, Harper and Row, 1982.

Proctor, D.F., I Anderson and G. Lundqvist. 1973. Clearance of inhaled particles from the human nose. Arch. Inter. Med. 131: 132.

Proctor, D.F. 1983. The nose, paranasal sinuses and middle ears. In: Allergy, Principles and Practice. Ed. E. Middleton, C.E. Reed and E.F. Ellis. C.V. Mosby Company, St. Louis, pp. 419-434.

Ritter, F.N. 1970. The vasculature of the nose. Ann. Otol. Rhinol. Laryngol. 79: 468.

Solomon, W.R. 1984 (A). Uncovering the "fine details" of pollen allergen transport. J. Allergy Clin. Immunol. 74: 674.

Solomon, W.R. 1984 (B). Aerobiology of pollinosis. J. Allergy and Clin. Immunol. 74: 449-461.

Stoksted, P. 1953. Rhinomonometric measurements for determination of the nasal cycle. Acta otolaryngology. (Stockh.) 82: 159.

Physiology and Allergic Pathophysiology

Arora, N. and S.V. Gangal. 1992. Efficacy of lipsome entrapped allergen in down regulation of IgE response in mice. J. Clin. Exper. Allergy. 22(1):35-42.

Baird, B., R.J. Shopes, V.T. Oi, J. Erickson, P. Kane and D. Holowka. 1989. Interaction of IgE with its high-affinity receptor. Structural basis and requirements for effective cross-linking. Intl. Archives Allergy & Appl. Immunol. 88(1-2): 23-8/

Bentley, A.M., M.R. Jacobson, V. Cumberworth, J.R. Barkans, R. Moqbel, L.B. Schwartz, A.M. Irani, A.B. Kay and S.R. Durham. 1992. Immunohistology of the nsasl mucosa in seasonal allergic rhinitis: increases in activated eosinophils and epithelial mast cells. J. Allergy Clin. Immunol. 89(4): 877-83.

Brunet, C., P. M. Bedard, A. Lavoie, M. Jobin and J. Hebert. 199. Allergic rhinitis is ragweed pollen. II. Modulation of histamine-releasing factor production by specific immunotherapy. J. Allergy Clin. Immunol. 89(1 Pt 1): 87-94.

Brunet, C., P.M. Bedard, A. Lavoie, M. Jobin and J. Hebert. 1992. Allergic rhinitis to ragweed pollen. I. Reassessment of the effects of immunotherapy on cellular and humoral responses. 89(1 Pt 1): 76-86.

Conrad, D.H., C.M. Squire, W.C. Bartlett and S.E. Dierks. 1991. Fc epsilon receptors. Current Opinion in Immunol. 3(6): 859-64.

Corren, J., A.D. Adinoff and C.G. Irvin. 1992. Changes in bronchial responsiveness following nasal provocation with allergen. J. Allergy Clin. Immunol. 89(2): 599-610.

Davies, R.J. 1991. Mast cells and allergic rhinitis. Clin. Exper. Allergy. 21 Suppl 1: 248-52.

de Vries, J.E., J.F. Gauchat, G.G Aversa, J. Punnonen and H. Gascan. 1991. Regulationof IgE synthesis by cytokins. Current Opinion in Immunol. 3(6): 851-8.

Denburg, J.A. 1991. Basophils, mast cells and eosinophils and their precursors in allergic rhinitis. Clin. Exper. Allergy. 21 Suppl 1: 253-8.

Drake-Lee, A.B., B. Moriarty and L.A. Smallman. 1991. Mast cel numbers i the mucosa of the inferior turbinate in patients with perennial allergic rhinitis: a light microscpic study. J. Laryngology & Otology. 105(9): 736-8.

Eiseman, E. and J.B. Bolen. 1992. Engagement of the high-affinity IgE receptor activates src protein-related tyrosine kinases. Nature. 355(6355): 78-80.

Fokkens, W.J., A.F. Holm, E. Rijntjes, P.. Mulder and T.M. Vroom. 1990. Characeterization and quantification of cellular infiltrates in nasal mucosa of patients with grass pollen allergy, non-allergic patients with nasal polyps and controls. Intl. Arch. Allergy & Appl. Immunol. 93(1): 66-72.

Haba, S. and A. Nisonoff. 1990. Inhibition of IgE synthesis by anti-IgE: role in long-term inhibition of IgE synthesis by neonatally administered soluble IgE. Proc. Ntl. Acad. Sci. U.S.A. 87(9): 3363-7.

Hakimi, J., C. Seals, J.A. Kondas, L. Pettine, W. Danho and J. Kochan. 1990. The alpha subunit of the human IgE receptor (FcERI) is sufficient for high affinity IgE binding. J. Biol. Chem. 265(36): 22079-81.

Heusser, C.H., J. Bews, V. Brinkmann, G. Delespesse, E. Kilchherr, F. Ledermann, G. Le Gros and K. Wagner. 1991. New concepts of IgE regulation. Intl. Achives Allergy App. Immunol. 94(1-4): 87-90.

Howard, F.D., H.R. Rodewald, J.P. Kinet and E.L. Reinherz. 1990. CD3 zeta subunit can substitute for the gamma subunit of Fc epsilon receptor type I in assembly and functional expression of the high-affinity IgE receptor: evidence for interreceptor complementation. Proc. Ntl. Acad. Sci. U.S.A. 87(18): 7015-9.

Jakschik, B.A., S. Falkenhein, and C.W. Parker. 1977. Precursor role of arachidonic acid in release of slow reacting substance from rat basophilic leukemia cells. Proc. Natl. Acad. Sci. USA 74: 4577.

Keegan, A.D., J.H. Peirce, J. Artrip, M. Plaut and W.E. Paul. 1991. Ligand stimulation of transfected and endogenous growth factor receptors enhances cytokin production by mast cells. Embo J. 19(12): 3675-82.

Kennerly, D.A., T.J. Sullivan and C.W. Parker. 1979a. Activation of phospholipid metabolism during mediator release from stimulated mast cells. J. Immunol. 12: 152-159.

Kennerly, D.A., C.J. Secosan, C.W. Parker and T.J. Sullivan. 1979c. Modulation of stimulated phospholipid metabolism in mast cells by pharmacologic agents that increase cAMP levels. J. Immunol. 123: 1519.

Kennerly, D.A., T.J. Sullivan, P. Sylweser, and C.W. Parker. 1979b. Diacylglycerol metabolism in mast cells: A potential role in membrane fusion and arachidonic acid release. J. Exp. Med. 150: 1039-1044.

Lee, T.H. 1989. Asthma and allergic rhinitis. Cur. Opin. Immunol. 1(4): 654-7.

Lewis, R.A. and K.F. Austen. 1984. The biologically active leukotrienes. J. Clin. Invest. 73: 889-897.

Lewis, R.A., N.A. Sorter, P.T. Diamond, K.F. Austen, J.A. Oates and L. J. Roberts. 1982. Prostaglandin D_2 generation after activation of rat and human mast cells with IgE. J. Immunol. 129: 1627-1631.

Linder, A., K. Strandberg and H. Deuschl. 1988. Variations in histamine concentration in nasal secretion in patients with allergic rhinitis. Allergy. 43(2): 119-26.

Liu, F.T., K. Albrandt, M.W. Robertson. 1988. cDNA heterogeneity suggests structural variants related to the high-affinity IgE receptor. Pro. Ntl. Acad. Sci. U.S.A. 85(15): 5639-43.

Lohse, M.J., K.N. Klotz, M.J. Salzer and U. Schwabe. 1988. Adenosine regulates the Ca2+ sensitivity of

mast cell mediator release. Pro. Ntl. Acad. Sci. U.S.A. 85(23): 8875-9.

MacGlashan, D.W., R.P. Schleimer, S.P. Peters, E.S. Schulman, G.K. Adams, H. Newball and L.M. Lichtenstein. 1982. Generation of leukotrienes by purified lung mast cells. J. Clin. Invest. 70: 747-751.

Marquardt, D.L. and S.I. Wasserman. 1983. Modulation of rat serosal mast cell biochemistry by in vivo dexamethasone administration. J. Immunol. 131: 934-939.

Marquardt, D.L., L.L. Walker, and S.I. Wasserman. 1984. Adenosine receptors on mouse bone marrow-derived mast cells: functional significance and regulation by aminophylline. J. Immunol. 133: 932-937.

Metzger, H., J.P. Kinet, U. Blank, L. Miller and C. Ra. 1989. The receptor with high affinity for IgE. Ciba Foundation Symposium. 147: 93-101; discussion 101-13.

Muir, D.C.F. 1972. Clinical Aspects of Inhaled Particles. Heinemann, London.

Murphy, R.C., S. Hammarstrom, and B. Samuelsson. 1979. Proc. Natl. Acad. Sci. USA 76: 4275-4279.

Naclerio, R.M., F.M. Baroody and A.G. Togias. 1991. The role of leukotrienes in allergic rhinitis: a review. Am. Rev. Resp. Dis. 143(5 Pt 2): S91 -5.

Okuda, M., H. Otsuka, K. Sakaguchi, M. Onishi and K. Okubo. 1989. Effect of anti-allergic treatment on nasal surface basophilic metachromatic cells in allergic rhinitis. Allergy Proc. 19(1): 23-6.

Rabenstein, D., R. Ludowyke and D. Lagunoff. 1985. Analysis of proton NMR spectrum and intramast cell histamine. Fed. Proc. 44: (Abst. #7435).

Raphael, G.D., Y. Igarashi, M.V. White and M.A. Kaliner. 1991. The pathophysiology of rhinitis. V. Sources of protein iin allergen-induced nasal secretions. J. Allergy Clin. Immunol. 88(1): 33-42.

Raphael, G.D., H.M. Duce, R. Wright, M.A. Kaliner. 1985. Methacholine-induced histamine release in nasal secretions. J. Allergy and Clin. Immunol. 75: (abst. #29).

Robertson, M.W., V.S. Mehl, M.L. Richards and F.T. Liu. 1991. mRNA variants encoding multiple forms of the high-affinity IgE receptor alpha subunit in transformed and nontransformed mast cells. Intl. Archives Allergy & App. Immunol. 96(4): 289-95.

Robertson, M.W. and F.T. Liu. 1988. IgE structure-function relatinships defined by sequence directed antibodies induced by synthetic peptides. Molecular Immunol. 25(2): 103-13.

Romagnani, S. 1990. Regulation and deregulation of human IgE synthesis. Immunology Today. 11(9): 316-21.

Rucci, L., E. Masini, R. Arbi Riccardi, E. Giannella, C. Fioretti, P.F. Mannaioni, M.B. Borghi Cirri and O. Fini Storchi. 1989. Vidian nerve resection, histamine turnover and mucosal mast cell function in patients with chronic hypertrophic non-allergic rhinitis. Agents & Actions. 28(3-4): 224-30.

Ruhno, J., K. Howie, M. Anderson, B. Andersson, M. Vanzieleghem, D. Hitch, P. Lapp, J. Denburg and J. Dolovich. 1990. The increased number of epithelial mast cells in nasal polyps and adjacent turbinates is not allergy-dependent. Allergy. 45(5): 370-4.

Schleimer, R.P., D.W. MacGlashan, S.P. Peters, N. Naclerio, D. Proud, N.F. Adkinson, L.M. Lichtenstein. 1984. Inflammatory mediators and mechanisms of release from purified human basophils. J. Allergy and Clin. Immunol. 74: 473-481.

Skoner, D.P. and L. Lee, W.J. Doyle, S. Boehm and P. Fireman. 1990. Nasal inflammaory mediators during natural pollen exposure. Annals of Allergy. 65(3): 206-10.

Stechschulte, D.J. 1990. Leukotrienes in asthma and allergic rhinitis. N.E. J. of Med. 323(25): 1769-70.

Stephan, V., M. Benhamou, J.S. Gutkind, K.C. Robbins and R.P. Siraganian. 1992. Fc epsilon RI-induced protein tyrosine phosphorylation of pp72 in rat basophilic leukemia cells (RBL-2H3). Evidence for a novel signal transduction pathway unrelated to G protein activation and phosphatidylinositol hydrolysis. J. Biological Chem. 267(8): 5434-41.

Stevens, R.L. and K.F. Austen. 1989. Recent advances in the cellular and molecular biology of mast cells. Immunol. Today. 19(11): 381-6.

Sullivan, T.J., K.L. Parker, A. Kulczycki and C.W. parker. 1976. Modulation of cyclic AMP unpurified rat mast cells. III. Studies on the effects of anti-IgE and concanavalin A on cyclic AMP concentrations during histamine release. J. Immunol. 117: 713-716.

Sullivan, T.J. and L.J. Brown. 1981. Roles of calcium in mediator release form mast cells. In: New Perspectives on Calcium.

Takai, Y., A. Kishimoto, Y. Kawahara, et al. 1981. Calcium and phosphatidylinositol turnover as signaling for transmembrane control of protein phosphorylation. Adv. Cyclic. Nuc. Res. 14: 301-313.

Takaishi, T., Y. Morita, K. Kido, and T. Miyamoto. 1984. Auranofin, an oral chrysotherapeutic agent, inhibits histamine release from human basophils. J. Allergy and Clin. Immunol. 74: 296-301.

Tepler, I., A. Shimizu and P. Leder. 1989. The gene for the rat mast cell high affinity IgE receptor alpha chain. Structure and alternative mRNA splicing patterns. J. Biol. Chem. 264(10): 5912-5.
Blank, U., C. Ra, L. Miller, K. White, H. Metzger and J.P. Kinet. 1989. Complete structure and expression in transfected cells of high affinity IgE receptor. Nature. 337(6203): 187-9.

Tepler, I., C.C. Morton, A. Shimizu, R.F. Holcombe, R. Eddy, T.B. Shows and P. Leder. 1989. The gene for the huma mast cell high-affinity IgE receptor alpha chain: chromosomal localization to Iq21-q23 and RFLP analysis. Am. J. Human Genetics. 45(5): 761-5.

Van de Heyning, P.H., J. Claes, J. Van Haesendonck, and M. Rosseel. 1991. A gap in surface therapy: topical antihistamines. Clin. Exper. Allergy. 21 Suppl 2: 21-7.

Vercelli, D. and R.S. Geha. 1989. The IgE System. Annals of Allergy. 63(1): 4-11.

Vercelli, D. and R.S. Geha. 1989. Regulation of IgE synthesis in humans. J. Clin. Immunol. 9(2): 75-83.

Vercelli, D. and R.S. Geha. 1991. Regulatio of IgE synthesis in humans: a tale of two signals. J. Allergy Clinical Immunol. 88(3 Pt1): 285-95.

Wasserman, S. 1983. Mediators of immediate hypersensitivity. Clin. Rev. Allergy 1: 309-349.

White, M.V. 1990. The role of histamine in allergic diseases. J. Allergy Clin. Immunol. 86(4 Pt 2): 599-605.

Wu, C.Y., M. Sarfati, C. Heusser, S. Fournier and M. Rubio-Trujillo. 1991. Glucocorticoids increase the synthesis of immunoglobulin E by interleukin 4-stimulated human lymphocytes. J. Clinical Invest. 87(3): 870-7.

Nasal Challenge Studies

Baumgarten, C.R., R.M. Naclerio, A.G. Togias, L.M. Lichtenstein, P.S. Norman, and D. Proud. 1985.

Kininogen in nasal secretions of allergic individuals. J. Allergy ad Clin. Immunol. 75: 30 (abst.).

Connel, J.R. 1968. Quantitative intranasal pollen challenge. J. Allergy 41: 123-139.

Corrado, O.J., E. Gomez, and R.J. Davies. 1985. Nasal mast cells: Characteristics and effect of allergen. J. Allergy and Clin. Immunol. 75: (abst. #184).

Fitzharris, P., R.J. Shaw, A.J. Wardlaw, O. Cromwell, A. Drake-Lee, and A.B. Kay. 1985. Sulphiodpeptide leukotrienes and LTB_4 in nasal secretions and nasal polyposis. J. Allergy and Clin. Immunol. 75: (abst. #31).

Kaliner, M., S.I. Wasserman, and K.F. Austen. 1973. Immunologic release of chemical mediators from human nasal polyps. N. Engl. J. Med. 289: 277.

McLean, J.A., A.A. Ciarkowski, W.R. Solomon, and K.P. Matthews. 1976. An improved technique for nasal inhalation challenge tests. J. Allergy Clin. Immunol. 57: 153-163.

Naclerio, R., A. Fogios, D. Proud, N.F. Adkinson, A. Kagey-Sobotka, M. Plaut, P.S. Norman, and L.M. Lichtenstein. 1985. Inflammatory mediators in nasal secretions during early and late reactions. J. Allergy Clin. Immunol. 73: 148 (abst.).

Newball, H.H., R.C. Talamo, and L.M. Lichtenstein. 1975. Release of leukocyte kallikrein mediated by IgE. Nature 254: 635.

Proud, D., A. Togias, R.N. Naclerio, S.A. Crush, P.S. Norman, L.M. Lichtenstein. 1983. kinins are generated in vivo following nasal airway challenge of allergic individuals with allergen. J. Clin. Invest. 72: 1678.

Clinical Aspects and Therapy

Aaronson, D.W. 1991. Comparative efficacy of H1 antihistamines. Annals of Allergy. 67(5): 5451-7.

Ancill, R.J., Y. Takahashi, Y. Kibune, R. Campbell, J.R. Smith. 1990. Randomized double-blind, placebo-controlled clinical trial of a selective 5-lipoxygenase inhibitor (AA-861) for the prevention of seasonal allergic rhinitis.

Araki, H. 1969. Clinical study on the effect of sodium aurothiomalate in bronchial asthma. Japan. J. Allergol. 18: 106.

Bayes de Luna, A., P. Coumel, J.F. Leclercq. 1989. Ambulatory sudden cardiac death: mechanisms of production of fatal arrhythmia o the basis of data from 157 cases. Am. Heart J. 117(1): 151-9.

Berman, B.A. 1988. Allergic rhinitis: mechanisms and management. J. Allergy Clin. Immunol. 81(5 Pt 2): 980-4.

Bernstein, J.M. 1992 The role of IgE-mediated hypersensitivity in the development of otitis media with effusion. Otolaryngologic Clin. No. America. 25(1): 197-211.

Blackwell, G., R. Carnuccio, M. DiRosa, R.J. Flower, L. Parente, P. Percio. 1980. Macrocortin: A polypeptide causing the antiphosphalipase effect of glucocorticoids. Nature (London) 289:147.

Borum, P., N. Mygind and F.S. Larsen. 1979. Intranasal ipratrpium: A new treatment for perennial rhinitis. Clin. Otolaryngol. 4: 407.

Bousquet, J., A. Hejjaoui and F.B. Michel. 1991. Recend advances in specific immunotheray for allergic rhinitis. Clin. Exper. Allergy. 21 Suppl 1: 259-61.

Brooks, C.D., A.L. Nelson, C. Metzler. 1984. Effect of flurbiprofen, a cyclooxygenase inhibiting drug, on induced allergic rhinitis. J. Allergy and Clin. Immunol. 73: 584-589.

Cohan, R.H., F.L. Bloom, R.B. Rhoades, H.J. Wittig, and L.D. Haugh. 1976. Treatment of perennial allergic rhinitis with cromolyn sodium. J. Allergy and Clin. Immunol. 58: 121-128.

de Weck, A.L. 1989. Conventional and new approaches to hyposensitization. Ciba Foundation Symposium 147: 254-9.

Doyle, W.J., D.P. Skoner, P. Fireman, J.T. Seroky, I. Green, F. Ruben, D.R. Kardatzke and J.M. Gwaltney. 1992. Rhinovirus 39 infection in allergic and nonallergic subjects. 89(5): 968-78.

Druce, H.M. and S. Goldstein, J. Melamed, J. Grossman, B.A. Moss and R.G. Townley. 1990. Multicenter placebo-conrolled study of nedocromil sodium 1% nasal solution in ragweed seasonal allergic rhinitis. Annals of Allergy. 65(3): 212-6.

Engler, D.B. and J.A. Grant. 1991. Allergic Rhinitis: a practical approach. Hospital Prac. 26(1): 105-8, 111-2.

Findlay, S., F. Huber, J. Garcia and L. Huang. 1992. Efficacy of once-a-day intranasal administration of triamcinolone acetonide in patients with seasonal allergic rhinitis. Annals of Allergy. 68(3): 228-32.

Georgitis, J.W., W.F. Clayto, J.I. Wypych, S.H. Barde, R.E. Reisman. 1984. Further evaluation of local nasal immunotherapy with aqueous and allergoid grass extracts. J. Allergy and Clin. Immunol. 74: 694-700.

Gleich, G.J., E.M. Zimmermann, L.L. Henderson and J.W. Yunginger. 1982. Effect of immunotherapy on immunoglobulin E and immunoglobulin G antibodies to ragweed antigens: A six year prospective study. J. Allergy and Clin. Immunol. 70: 261.

Grammer, L.C., M.A. Shaughnessy, I.M. Suszko, J.J. Shaughnessy, and R. Patterson. 1984. Persistence of efficacy after a brief course of polymerized ragweed antigen - A controlled study. J. Allergy Clin. Immunol. 73: 484-489.

Harris, D.M., L.E. Morton, and P. Jack. 1974. The effect of intranasal beclomethasone diproprionate on adrenal function. Clin. Allergy 4: 291.

Hirata, F., et al. 1981. Proc. Natl. Acad. Sci. USA 78: 3190.

Howarth, P.H. 1989. Allergic rhinitis: a rational choice of treatment. Respiratory Medicine. 83(3): 179-88.

Huerter, J.V., Jr. 1992. Functional endoscopic sinus surgery ad allergy. Otolaryngologic Clin. No. America. 25(1): 231-8.

Iliopoulos, O., D. Proud, N.F. Adkinson, Jr., P.S. Creticos, P.S. Norman, A. Kagey-Sobotka, L.M. Lichtenstein and R.M. Naclerio. 1991. Effects of immunotherapy on the early, late, and rechallenge nasal reaction to provocation with allergen: changes in inflammatory mediators and cells. J. Allergy Clin. Immunol. 87(4): 855-66.

Kaliner, M.A. 1992. Nonsedating antihistamines: pharmacology, clinical efficacy and adverse effects. Am. Family Physician. 45(3): 1337-42.

Kaulbach, H.C., Y. Igarashi, J. Mullol, M.V. White and M.A. Kaliner. 1992. Effects of nedocromil sodium on allergen-induced rhinitis in humans. J. Allergy Clin. Immunol. 89(2): 599-610.

Kobayashi, R.H., D.G. Tinkelman, M.E. Reese, R.S. Sykes and G.E. Pakes. 1989. Beclomethasone

dipropionate aqueous nasal spray for seasonal allergic rhinitis in children. Annals of Allergy. 62(): 205-8.

Koda, A., Y. Yanagihara and N. Matsuura. 1991. IPD-1151T: a prototype drug for IgE antibody synthesis modulation. Agents & Actions. 34: 369-78.

Li, J.R., J.W. Yunginger, C.E. Reed, H.S. Jaffe, D.R. Nelson, G.J. Gleich. 1990. Lack of suppression of IgE production by recombinant interferon gamma: a controlled trial in patients with allergic rhinitis. J. Allergy Clin. Immunol. 85(5): 934-40.

Lichtenstein, L.M., P.S. Norman and K. Ishizaka. 1974. Studies on the immunological basis for the clinical effects of immunotherapy. In: Allergology. Proceedings of the VIII International Congress of Allergology. Ed. Y. Yamamura et al., Excerpta Medica, Amsterdam.

Lowell, F.C. and W. Franklin. 1963. A "double blind" study of treatment with aqueous allergenic extracts in cases of allergic rhinitis. J. Allergy 34: 165.

Mabry, R.L. 1992. Topical pharmacotherpay for allergic rhinitis: new agents. So. Med. J. 85(2): 149-54.

Mansmann, H.C., Jr., J. Rosen, R. Ziering, F. Hampel, P. Ratner, S. Findlay, W. Kniker, Z. Haddad and A. Daigle. 1991. Pentigetide nasal solution: a multicenter study evaluating efficacy and safety in patients with seasonal allergic rhinitis. Annals of Allergy. 67(4): 409-15.

Mathews, D.R., B. McNutt, R. Okerholm, M. Flicker and G. McBride. 1991. Torsades de pointes occurring in association with terfenadine use [letter; comment]. JAMA. 266(17): 2375-6.

McTavish, D., K.L. Goa, M. Ferrill. 1990. Terfenadine. Anupdated review of its pharmacological properties and therapeutic efficacy. Drugs. 39(4): 552-74.

Middleton, E., Jr. 1988. Chronic rhinitis in adults. J. allergy Clin. Immunol. 81(5 Pt 2): 971-5.

Mitchell, E.B., S. Wilkins, J. McCallum Deighton, and T.A.E. Platts-Mills. 1985. House dust mite reduction in the home: Use of an acaracide. J. Allergy Clin. Immunol. 75: (abst. #166).

Mullarkey, M.F. 1988. Eosinophilic nonallergic rhinitis. J. Allergy Clin. Immunol. 82(5 Pt 2): 941-9.

Mygind, N. C.B. Pedersen, S. Prytz, and M. Sorenson. 1975. Treatment of nasal polyps with intranasal beclomethasone diproprionate aerosol. Clin. Allergy 5: 159.

Mygind, N., B. Weeke, A. Dirksen and N.J. Johnsen. 1978. Perennial rhinitis. Clin. Otolaryngol. 3: 189.

Naclerio, R.M. 1991. Allergic rhinitis. New Eng. J. Med. 325(12): 860-9.

Nair, N., D. Lang, S. Wong, S.J. Weiss, A. Bewtra, R.G. Townley. A double-blind randomized evaluation of astemizole in comparison with placebo in the treatment of seasonal allergic rhinitis. J. Allergy and Clin. Immunol. 75: (abst. #247).

Nathan, R.A., E.A. Bronsky, P. Fireman, J. Grossman, C.F. LaForce, R.F. Lemanske, Jr., D.S. Pearlman, P.H. Ratner and P.R. Rogenes. 1991. Once daily fluticasone proprionate aqueous nasal spray is an effective treatment for seasonal allergic rhinitis.

Nelson, H.S. 1983. Diagnostic procedures in allergy. I. Allergy skin testing. Annals Allergy 51: 411-417.

Norman, P.S. 1983. Review of nasal therapy: Update. J. Allergy Clin. Immunol. 72: 421-432.

Okuda, M., and N. Myngind. 1980. Effects of beclomethasone diproprionate nasal spray on subjective and objective findings in perennial and allergic rhinitis. Clin. Otolaryngol. 5: 315.

Ortolani, C., E. Pastorello, Et al. 1984. Grass pollen immunotherapy: a single year double-blind, placebo-controlled study in patients with grass pollen-induced asthma and rhinitis. J. Allergy and Clin. Immunol. 73: 283-290.

Otsuka, H., A. Mezawa, M. Ohnishi, K. Okubo, H. Seki and M. Okuda. 1991. Changes in Nasal metachromatic cells during allergen immunotherapy. Clin. Exper. Allergy. 21(1): 115-9.

Pelikan, Z. and M. Pelikan-Filpek. 1982. The effects of disodium cromoglycate and beclomethasone diproprionate on the immediate response of the nasal mucosa to allergen challenge. Ann. Allergy 40: 283-292.

Poothullil, J., C. Umemoto, J. Dolovich, F.E. Hargreave, R.P. Day. 1976. Inhibition by prednisone of late cutaneous allergic responses induced by antiserum to human IgE. J. Allergy Clin. Immunol. 57: 164.

Rangi, S.P., M.H. Serwonska, G.A. Lenahan, W.C. Pickett, V.A. Blake, S. Sample and E.J. Goetzl. 1990. Suppression by ingested eicosapentaenoic acid of the increases in nasal mucosal blood flow and eosinophilia of ryegrass-allergic reactions. J. Allergy Clin. Immunol. 85(2): 484-9.

Reisman, R.E., P.M. Mauriello, G.B. Davis, J.W. Georgitis and J.M. DeMasi. 1990. A double-blind study of the effectiveness of a high-efficiency particulate air (HEPA) filter in the treatment of patients with perennial allergic rhinitis and asthma. J. Allergy Clin. Immunol. 85(6): 1050-7.

Ruhno, J., J. Denburg and J. Dolovich. 1988. Intranasal nedocromil sodium in the treatment of ragweed-allergic rhinitis. J. Allergy Clin. Immunol. 81(3): 570-4.

Schatz, M. and R.S. Zeiger. 1990. Treatment of Asthma and allergic rhinitis during pregnancy. Annals of Allergy. 65(6): 427-9.

Simons, F.E. 1990. New H1-receptor antagonists: clinical pharmacology. Clin. Exper. Allergy. 20 Suppl 2: 19-24.

Slavin, R.G. 1988. Sinusitis in adults and its relation to allergic rhinitis, asthma, and nasal polyps. J. Allergy Clin. Immunol. 82(5 Pt2): 950-6.

Storms, W., E. Bronsky, S. Findlay, D. Pearlman, S. Rosenberg, G. Shapiro, L. Southern, D. Tinkelman, S. Weakley, M. Welch, et al. 1991. Once daily triamcinolone acetonide nasal spray is effective for the treatment of perennial allergic rhinitis. Annal of Allergy. 66(4): 329-34.

Tarlo, S.M., D.W. Cockcroft, J. Dolovich and F.E. Hargreave. 1977. Beclomethasone diproprionate in perennial rhinitis. J. Allergy and Clin. Immunol. 59: 232-236.

Turkeltaub, C., P.S. Norman, J.D. Johnson, S. Crepea. Treatment of seasonal and perennial rhinitis with intranasal flunisolide. Allergy 37: 303-311.

Twarog, F.J., F.J. Picone, R.S. Strunk, J. So, and H.R. Colten. 1977. Immediate hypersensitivity to cockroach. J. Allergy and Clin. Immunol. 59: 155.

Viner, A.S. and N. Jackman. 1976. Retrospective survey of 1271 patients diagnosed as perennial rhinitis. Clin. Allergy 6: 251.

Walker, C.L. 1992. Allergic rhinitis: a review. Comprehensive Therapy. 18(3): 11-3.

Complications

Ackerman, M.N., R.A. Friedman, W.J. Doyle, C.D. Bluestone and P. Fireman. 1984. Antigen-induced

eustachian tube obstruction. An intranasal provocative challenge test. J. Allergy and Clin. Immunol. 73: 604-609.

Kaufman, J., J.C. Chen, and G.W. Wright. 1970. The effect of trigeminal resections on reflex bronchoconstriction after nasal and nasopharyngeal irritation in man. Am. Rev. Respir. Dis. 101: 768.

Kaufman, J. and G.W. Wright. 1969. The effect of nasal and nasopharyngeal irritation on airway resistance in man. Am. Rev. Resp. Dis. 100: 626-630.

Schumacher, M.J., K.A. Cota, L.M. Taussig. 1985. Study of naso-bronchial reflex in allergic rhinitis with asthma. J. Allergy and Clin. Immunol. 75: (abst. #148).

From the NIH

National Institutes of Health

How to Create a Dust-Free Bedroom

Dust-sensitive individuals, especially those with allergies and asthma, can reduce some of their misery by creating a "dust-free" bedroom. Dust may contain dander, molds, and fibers as well as tiny mites. These mites, which also live in bedding, upholstered furniture, and carpets, thrive in the summer and die in the winter. The particles seen floating in a shaft of sunlight are dead dust mites and their waste products; the waste products actually provoke the allergic reaction.

Most people cannot control the dust conditions under which they work or spend their daylight hours. But everyone can, to a large extent, eliminate dust from the bedroom. To create a dust-free bedroom, reduce the number of surfaces on which dust can collect. Dr. Michael Kaliner, head of the Allergic Diseases Section, National Institute of Allergy and Infectious Diseases, suggests the following guidelines:

❑ Steam or hot water heat is preferable to hot air heat. If there is a hot air furnace outlet in the room, install a dust filter made of several layers of cheesecloth or some other adequate material (old nylon hose); change the filter frequently. Seal holes or cracks in the floor around heating or other pipes with adhesive tape, although for some cracks transparent tape is adequate. In addition, change or clean furnace and air-conditioning filters every 2 to 4 weeks.

❑ Completely empty the room, just as if one were moving. Empty and clean all closets and, if possible, store contents elsewhere and seal closets. If this is not possible, keep clothing in zippered plastic bags and shoes in boxes off the floor. Give the woodwork and floors a thorough cleaning and scrubbing to remove all traces of dust. Wipe wood, tile, or linoleum floors with water, wax, or oil. If linoleum is used, cement it to the floor.

❑ Keep only one bed in the bedroom. Encase box springs and mattress in a dust-proof cover (zippered plastic). Scrub bed springs outside the room. If a second bed must be in the room, prepare it in the same manner.

❑ Carpeting makes dust control impossible. Although shag carpets are the worst type for the dust-sensitive person, all carpets trap dust. Therefore, hardwood, tile, or linoleum floors are preferred. Washable throw rugs may be used.

❑ Use a dacron mattress pad and pillow. Avoid fuzzy wool blankets or feather- or wool-stuffed comforters; use only washable materials on the bed. Launder sheets and blankets frequently.

❑ Keep furniture and furnishings to a minimum. Avoid upholstered furniture and venetian blinds. A wooden or metal chair that can be scrubbed may be used in the bedroom. If desired, hang plain, lightweight curtains on the windows. Wash the curtains once a week.

❑ Clean the room daily. Do a thorough and complete cleaning once a week: clean the floors, furniture, tops of doors, window frames, sills, etc., with a damp cloth or oil mop; air the room thoroughly; then close the doors and windows until the dust-sensitive person is ready to occupy the room.

❑ Keep the doors and windows of the bedroom closed as much as possible, especially when not using the room. Use this room for sleeping only. Dress and undress and keep clothing in another room, if possible.

❑ If the dust-sensitive person is a child, do not keep toys that will accumulate dust in the room. Do not use stuffed toys at all; use only washable toys of wood, rubber, metal, or plastic, and store them in a closed toy box or chest.

❑ Keep all animals with fur or feathers out of the room.

❑ Try using room air cleaners fitted with high efficiency particulate activating (HEPA) filters to help control the dust.

While these steps may seem difficult at first, experience plus habit will make them easier. The results—better breathing, fewer medications, and greater freedom from allergy and asthma attacks—will be well worth the effort.

Prepared by:
Laurie K. Doepel
Office of Communications
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD 20892

January 1991

ALLERGIC RHINITIS

- A Potpourri of Important Concepts -

Donald Kennerly, MD, PhD

1. Allergic rhinitis is the most common chronic disease of young adults.
2. The mucosa in AR is pale, pale blue or normal pink; erythema suggests infection or rhinitis medicamentosa.
3. Nasal smears for eosinophils provides rapid support for a suspected diagnosis of AR and can quickly distinguish between a viral URI and an exacerbation of AR.
4. A full panel of RAST/PHAST/MAST tests costs more than a complete workup (Hx, PE, skin tests, nasal smear and PFTs) of the vast majority of Board Certified allergists.
5. Total IgE is of little or no value in differential diagnosis or perennial rhinitis.
6. Sensitivity to allergens (presence of allergen specific IgE) to confirm a diagnostic impression can be obtained by the regionally specific Quidel^{R} screening test.
7. The absence of prominent seasonal fluctuations in symptoms does not rule out AR.
8. The use of sedating antihistamines can cause significant morbidity and exposes patients to unnecessary risks; they should be used only in those who cannot afford nonsedating medications or in whom sedation is purposely sought.
9. Vigorous therapy of AR may dramatically reduce the severity of allergic asthma.
10. Recognition of pet sensitivity in perennial AR with subsequent avoidance is simple and effective; dust mite avoidance is more difficult; little data supports a role for filters in reducing symptoms.
11. Patient education regarding the <u>regular</u> use of topical nasal steroids is critical.
12. Concomitant use of topical decongestants (such as Afrin^{R}) and topical nasal steroids can improve patients complaining of residual <u>congestion</u> associated with AR.
13. Using intranasal Atrovent^{R} (with a baby bottle nipple "adapter") can dramatically improve patients complaining of residual <u>rhinorrhea</u> associated with AR.
14. AR can coexist with other causes of rhinitis. Especially consider chronic sinusitis, vasomotor rhinitis, rhinitis medicamentosa and pregnancy.
15. Development of asthma may not involve "classic" symptoms/signs -- watch for unexplained cough (especially nocturnal or post exercise) and post exercise dyspnea that does not resolve quickly.
16. Allergen immunotherapy is cost effeetive (compared to medications Rx) for patients with >6-9 months of AR annually who require frequent use of 2 or more Rx during symptomatic periods or for patients with >3-6 months of AR who use $\geq$ 3 Rx.