Derm-Allergy

Parkland Hospital

Internal Medicine Grand Rounds

ALLERGIC RHINITIS

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ALLERGIC RHINITIS - Contents

HISTORICAL PERSPECTIVES

Allergic rhinitis is a disorder of modern man. Unlike many diseases that can be traced to detailed ancient clinical descriptions, 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 the dissected messentery. However, it wasn't until 1878 that Paul Ehrlich first described the metachromatic staining pattern of "mastzellen" or mast cells as we call them today.

Along clinical lines 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 was unfortunately not popularized at that 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 initiated the first course of immunotherapy for seasonal rhinitis. That same year Dale 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, Prausnitz and Kustner demonstrated the passive transfer of immediate sensitivity by transfering serum from a patient with fish sensitivity. 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 antihistamine and with it the first pharmacologic treatment of allergic rhinitis became available. In 1953 Riley and 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 and demonstrated its specific binding to tissue mast cells and circulating basophils and ushered in the modern era of immediate hypersensitivity.

During the ensuing 15 to 20 years investigative efforts have been focused on two major areas in immediate hypersensitivity in the basic science arena. First, the 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 of 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. We are currently entering a time when the realistic control of allergic disorders may not only be possible but seems likely. It is quite possible that we may during the next generation bring to a close the major morbidity that allergic rhinitis brings to a large subpopulation of the industrialized world.

EPIDEMIOLOGY

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. Atopic diseases are 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).

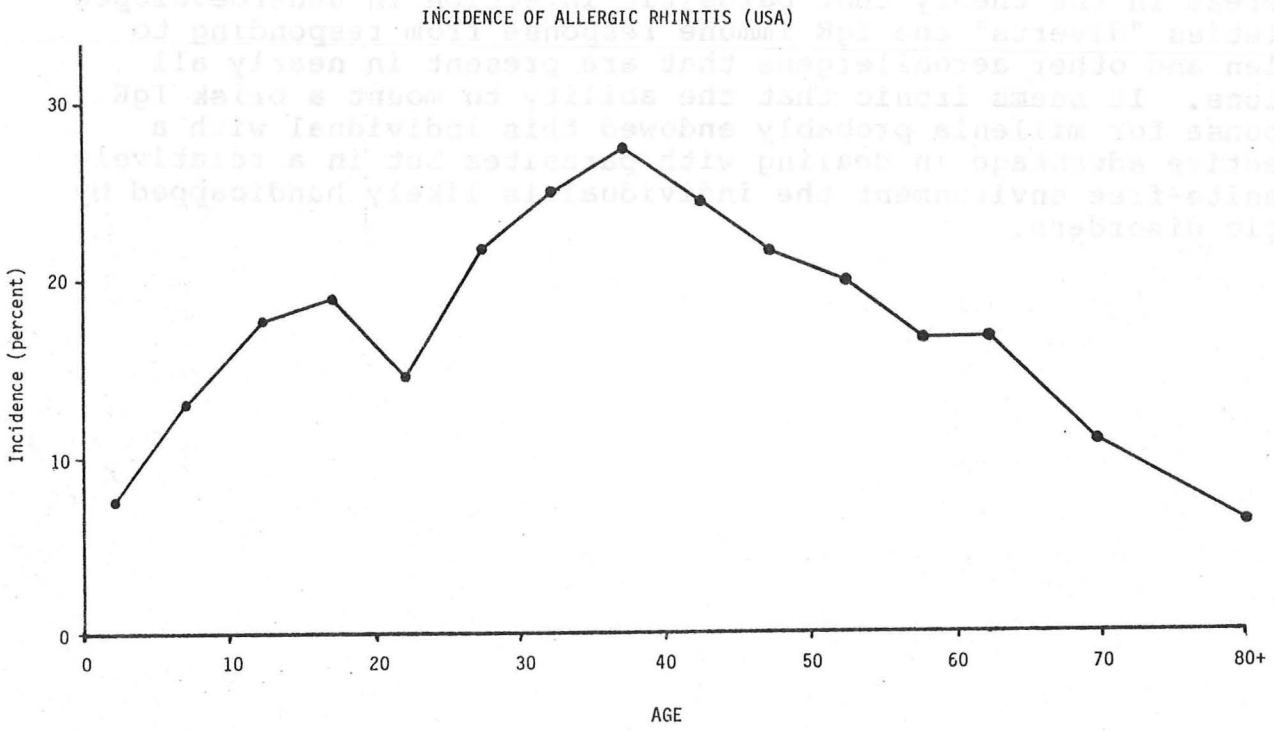


Figure 1

Allergic rhinitis because of its almost nonexistant mortality is largely ignored by physicians and often ineffectively treated. Only 75% of individuals affected by allergic rhinitis take medication but do so only approximately half the time that they

are symptomatic as a result of side effects imposed by their medication(s). Consequently, approximately two thirds of those suffering from allergic rhinitis feel that they are "bothered a great deal" by their symptoms (Hess and Lyon, 1985).

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 $2 billion and the value of nearly 3 million missed school days is inestimatable.

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 of allergic rhinitis and it would appear that the absence of a clinical description of this disorder 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 millenia probably endowed this individual with a selective advantage in dealing with parasites but in a relatively parasite-free environment the individual is likely handicapped by atopic disorders.

PATHOPHYSIOLOGY

Nasal Function

Figure 2 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 37°C air markedly reduced in particle density. 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 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

Vocal resonance

Olfaction

Figure 2

The vibrissae remove particles larger than 100 micron and the nasal mucosa removes nearly 100% of particles greater than 10 microns in size and 80% of those in the 5-10 micron range. Figure 3 demonstrates the effectivness of the nose in removing particles of varying diameter (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 ciliary action. The mucus blanket is moved posteriorly by ciliary transport and deposited into the nasopharynx and is entirely replaced approximately every 15 minutes (Proctor, 1973). Cultures at different locations 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) (Andersen et al., 1974). Figure 4 illustrates the sizes of a variety of particles present either in industrial or non work settings.

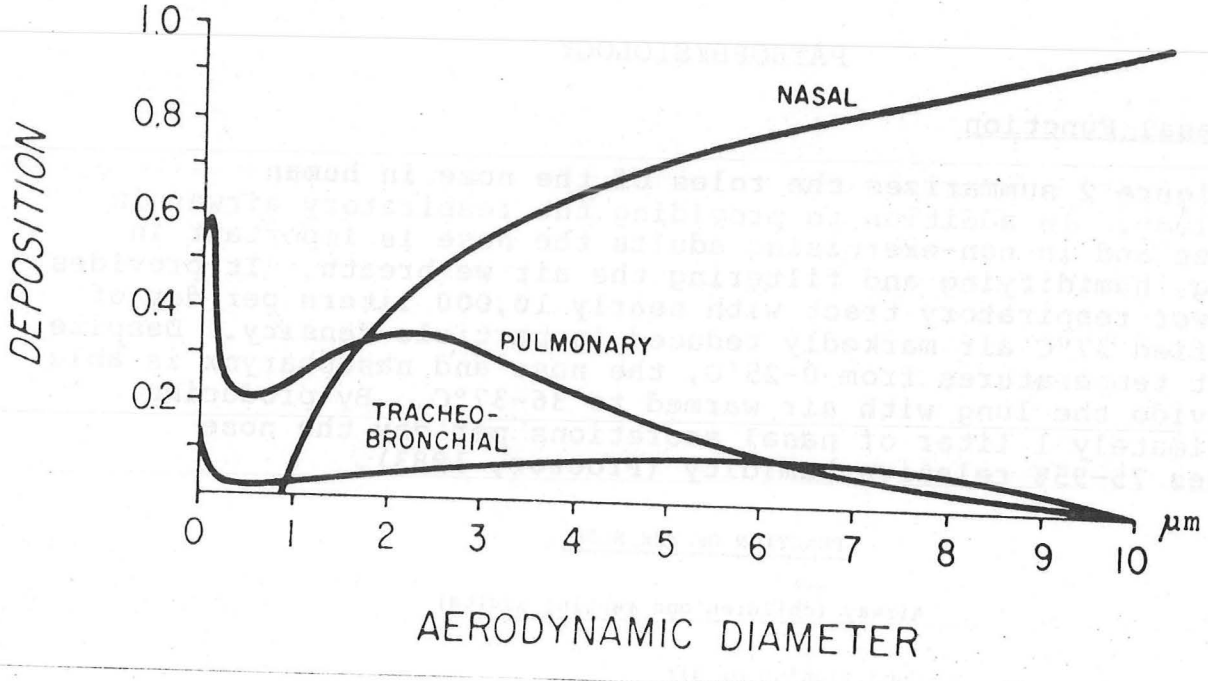


Figure 3

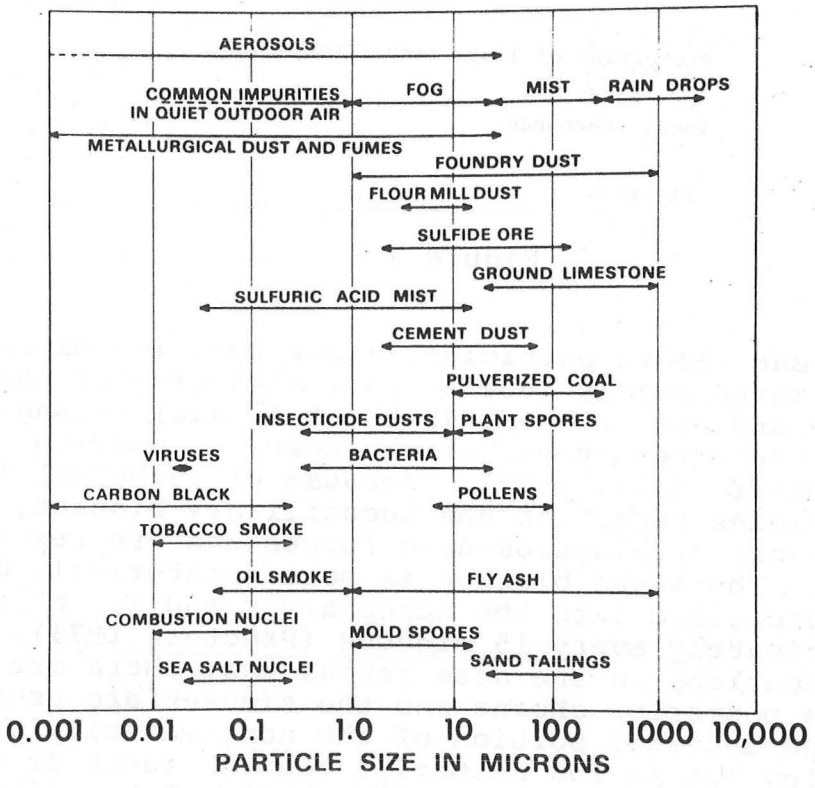


Figure 4

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 mucosa is composed of columnar cells that possess either microvilli or cilia and occasional goblet cells. Numerous glands present in the lamina propria secrete watery fluid. Mast cells are present in the epithelium and in perivascular areas.

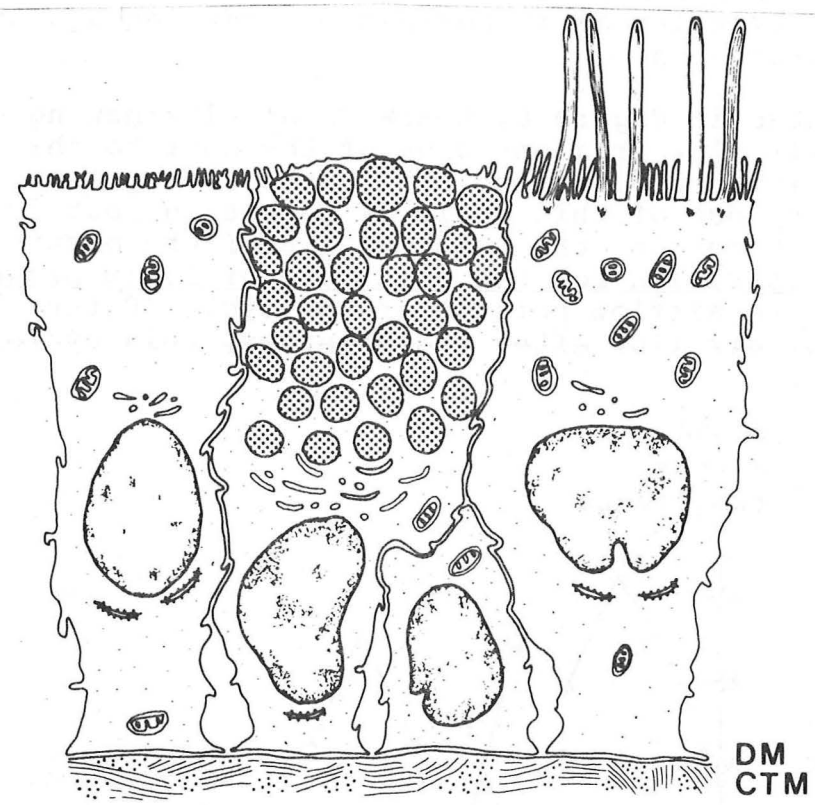


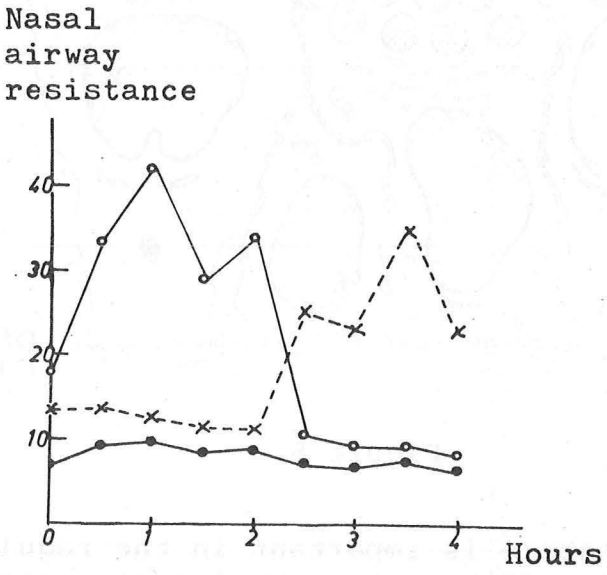
Figure 5

The nasal vasculature is important in the regulation of nasal airway resistance. In addition to normal tissue perfusion, the nasal mucosa is rich in capacitance beds (venous sinusoids) that are able to become engorged resulting in a 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 the venus sinusoids. Antihypertensive agents that interfere with alpha stimulation (guanethidine, bretyllium, aldomet, and reserpine) not infrequently produce nasal congestion as a side effect.

Parasympathetic innervation is provided by the facial nerve by way of 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.

As illustrated in Figure 6, there is an alternating cyclical obstruction to air flow from one side of the nose to the other over a 4 hour time period termed the "turbinate cycle" (Stoksted, 1953). The importance of this cycle is uncertain, but it is postulated that it permits the nasal mucosa of the obstructed side to recover in preparation for the high rate of fluid production required during the airflow portion of the cycle (Ritter, 1970). In the absence of air flow after tracheostomy, this cycle ceases.



Turbinate cycle. Alternating 'contraction' of homolateral and 'dilatation' of contralateral turbinates. Resulting changes in unilateral and in total nasal airway resistance are demonstrated by means of rhinomanometry. ● —— ●: Total nasal airway resistance. ○ —— ○: Unilateral nasal airway resistance. × —— ×: Contralateral nasal airway resistance. From Stoksted (1953). By courtesy of the author and *Acta oto-laryngologica (Stockholm)*.

Figure 6

Reflexes that are important to the maintainence of nasal homeostasis are illustrated in Figure 7. 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 the enhanced parasympathetic output. This represents a protective response to prevent introduction of noxious agents into the lower respiratory tract. Recent evidence suggests that the sensitivity of these reflexes is markedly enhanced during pollen season in patients with allergic rhinitis. In studies utilizing nasal challenge of patients with allergic rhinitis the artificial introduction of pollen causes within 2 to 4 hours a marked increase in reactivity of these reflexes (Connel, 1968). This enhanced sensitivity to nonspecific stimuli is not caused by exposure to irritants alone or histamine, suggesting that other mediators of immediate hypersensitivity confer this sensitivity. Whether this response is be brought about by neuronal hypersensitivity, enhanced epithelial permeability or alterations in the density of receptors is uncertain.

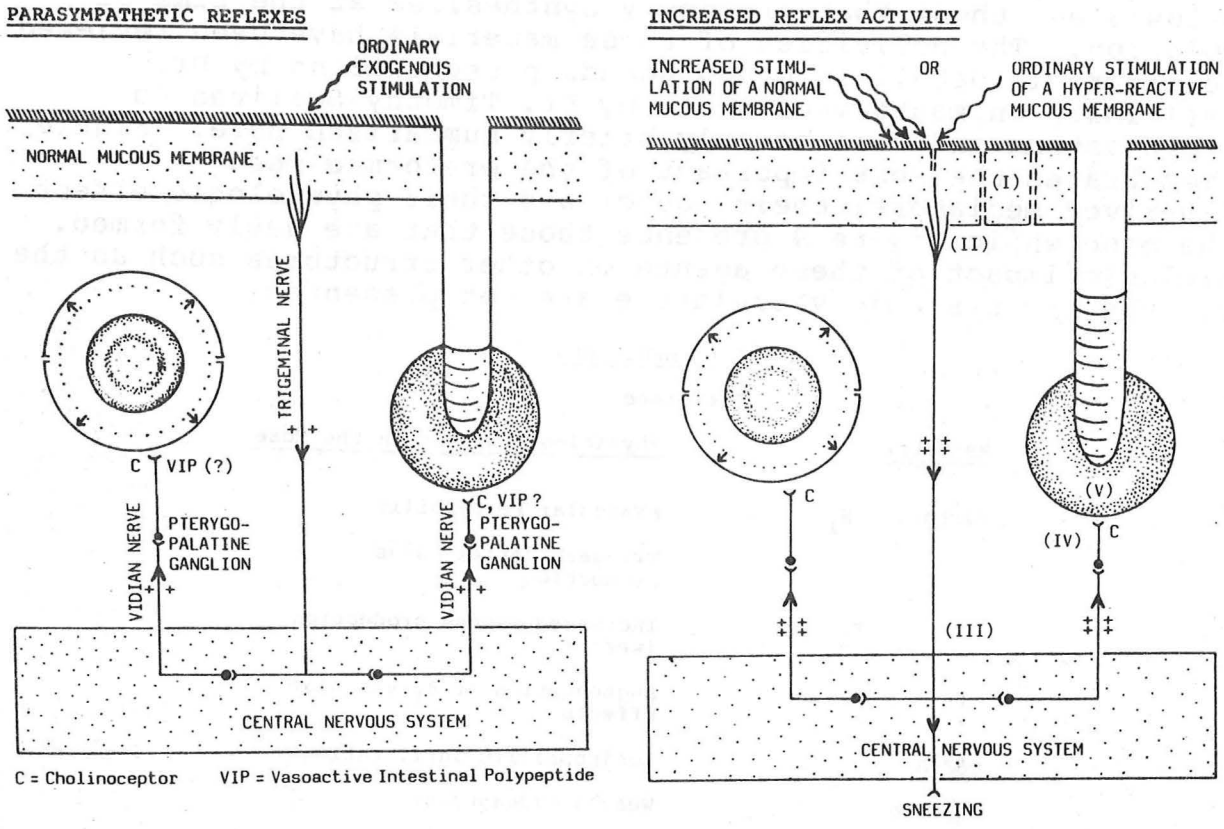


Figure 7

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"). However, 75 years passed before it was proven by Riley and West in 1953 that mast cells contain histamine. For nearly 50 years it hasbeen 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) that work became accellerated 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).

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. The activities of these materials have been reviewed in considerable detail in Grand Rounds presentations by Dr. Michael Tharp on mastocytosis and by Dr. Timothy Sullivan on allergic asthma and will be only briefly summarized here. Figure 8 demonstrates the most important of the preformed mast cell-derived mediators, their source and their physiologic effect in the nose while Figure 9 presents those that are newly formed. Physiologic impact of these agents on other structures such as the skin, lung and systemic vasculature are not presented.

MAST CELL MEDIATORS

Preformed

Mediator	Physiologic Effect in the Nose
Histamine H_1	↑Vascular Permeability
	Triggers reflex mucus production
H_2	Increased mucous production (weak)
	Augmentation of H_1 vascular effects
ECF-A	Eosinophillic infiltration
Heparin	Weak anticoagulent
	Binds histamine
NCF	Neutrophillic infiltration

Figure 8

MAST CELL MEDIATORS

Newly Synthesized

Mediator	Source	Physiologic Effect in the Nose
LTC_4	Arachidonate	Mucus Production ↑Vascular Permeability
PGD_2	Arachidonate	↑Vascular Permeability
TXB_2	Arachidonate	Platelet Activation
PAF (AGEPC)	Phospholipid	Platelet Activation Neutrophil Activation Vascular Permeability
Kinins	Kininogen (via MC kallikrein)	↑Vascular Permeability

Figure 9

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. Histamine is formed by the decarboxylation of the amino acid histidine by the enzyme histidine decarboxylase. Histamine is stored in electron dense secretory granules in the mast cell and in the basophil and is ionically coupled to the highly negatively charged polysaccharide and to neutral proteases. In the mast cell granule the concentration of histamine is approximately 0.41 M (Rabenstein et al., 1985) resulting in extraordinarily high levels of histamine in the area surrounding secreting mast cells, perhaps making the observation that systemic antihistamines are of only modest efficacy not surprising. Introduction of aerosols containing histamine produces sneezing, nasal puritis, nasal obstruction and watery rhinorrhea. It does not produce an eosinophil containing rhinorrhea nor does it enhance sensitivity to non-specific noxious agents. Histamine acts not only in a direct H_1 fashion on the local vasculature (causing small anteriolar and small venular dilation and post capillary venule permeability) but exerts significant effects by initiating the reflexes described previously. H_2 vascular mechanisms are modest but H_2 antagonists do modestly improve the inhibition by H_1 antagonists of histamine-mediated nasal obstruction. Unilateral introduction of histamine produces only minimal and transient contralateral nasal obstruction indicating the weakness of reflex vasodilation. The importance of histamine in stimulating reflex nasal secretion is illustrated by the observation that unilateral introduction of histamine or antigen produces secretion on the contralateral side equivalent to approximately 60% of that observed on the homolateral side. This contralateral secretion is blocked effectively by homolateral

topical H_1 antihistamines supporting the concept that sensory fibers seem likely to be H_1 histamine sensitive (Mygind, 1982). H_2 receptors are able to cause only modest direct enhancement of mucus secretion.

ECF-A. The two tetrapeptides (ECF-A) that cause eosinophil chemotactic activity are contained in mast cell granules and have been known for some time to elicit intense eosinophilic infiltration. The role of eosinophils in the nose or nasal secretions is uncertain but the ability of eosinophils to release a protein (major basic protein) that causes significant epithelial destruction, may be of significant physiological importance.

Other preformed mediators include heparin, which in man is only a weak anticoagulant, and of uncertain importance aside from its ability to bind histamine in the secretory granule. Neutrophil chemotactic factor (NCF) is able to cause neutrophilic infiltration *in vitro* (Oertel and Kaliner, 1981), however, neutrophils are an inconsistent finding in the nasal secretion in patients with allergic rhinitis. A late phase of IgE mediated secretion sometimes occurs 4-18 hours after antigen exposure and usually is characterized by neutrophilic infiltration suggesting that plays an important role in this response. A host of other materials including neutral proteases and glycosidases have been described to be contained in the mast cell granule but their physiologic importance is less certain.

Prostaglandin D_2 (PGD_2). After arachidonic acid is released from mast cell lipid stores it is rapidly converted via the cyclooxygenase and subsequent enzymes to produce PGD_2 (Lewis et al., 1982), as illustrated in Figure 10. This prostaglandin is the major arachidonic acid product in the mast cell and has important physiologic effects including enhancement of vascular permeability. Interestingly the basophil appears not to be able to synthesize PGD_2.

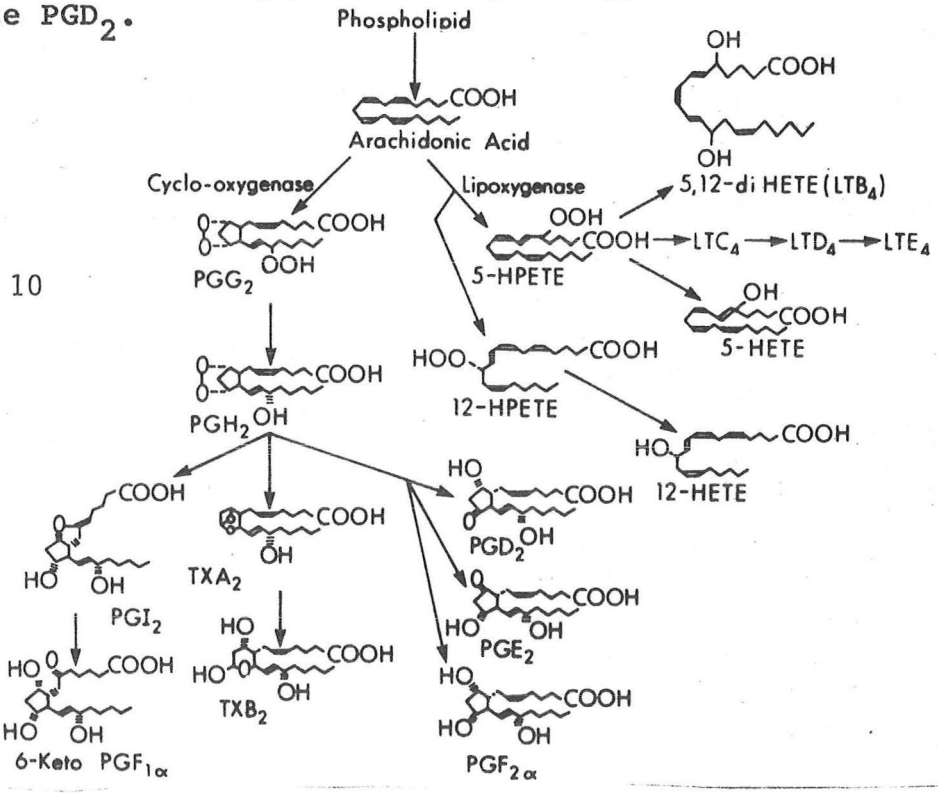


Figure 10

Leukotriene C_4 (LTC_4) - LTC_4 is formed from a hydroperoxy derivative of arachidonic acid (5-HPETE) and glutathione (Lewis and Austen, 1984) by human mast cells (MacGlashan et al., 1982) and is able to cause direct enhancement of mucous secretion and vascular permeability. Unlike the lung the ability of LTC_4 to cause smooth muscle contraction is of minimal importance in the nose. Of some interest is the observation that the relative synthesis of LTC_4 compared to PGD_2 is reduced in stimulated nasal polyp tissue compared to pulmonary derived tissue.

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 may in part be 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 and neutrophil activation. HETE has been shown to be produced by mast cells but its role in nasal physiology is yet to be determined.

Mediator Impact on Nasal Physiology

When mast cells are stimulated by antigen-induced crosslinking of mast cell IgE receptors to secrete or synthesize histamine, PGD_2, leukotriene C_4, PAF, and kinins a number of physiologic consequences are initiated. Histamine and to an uncertain extent other mediators cause neuronal stimulation that results in glandular secretion and modest vasodilation and by direct mechanism causes marked small vessel vasodilation and increased vascular permeability. The end result is nasal obstruction secondary to vascular engorgement and edema and rhinorrhea - the classic presentation of patients with allergic rhinitis. ECFA is able to induce an eosinophil infiltration of nasal secretions.

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 nsensitive and varies from lab to lab and patient to patient for obvious anatomic reasons (McLean et al. 1976). The observation that mast cells contain histamine and are able <u>in vitro</u> to synthesize or secrete a variety of mediators and that nasal polyps obtained from allergic individuals were able to form these mediators was shown during the last 10 years (Kaliner et al., 1973). More recently, however, 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). Figure 11 demonstrates that the appearance of histamine, kinin, and TAME esterase activity (the latter as a marker of the ability to form kinins) are related to antigen dose in a ragweed sensitive patient (Naclerio et al., 1983). Figure 12 compares the placebo challenge to antigen challenge using several parameters. Leukotriene C4 and D4 released into in nasal secretions have recently 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% for control challenge (Corrado et al., 1985).

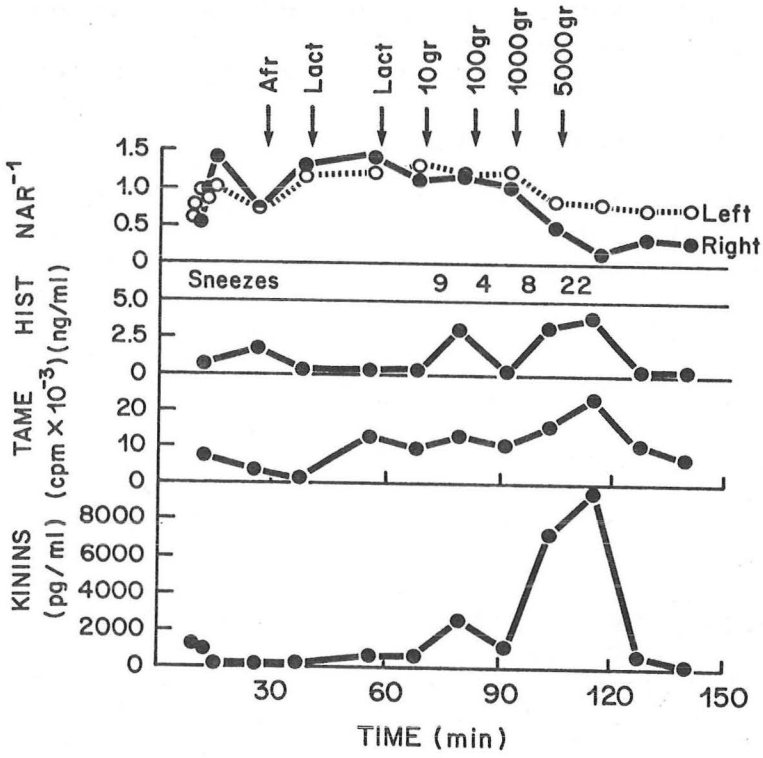


Figure 11

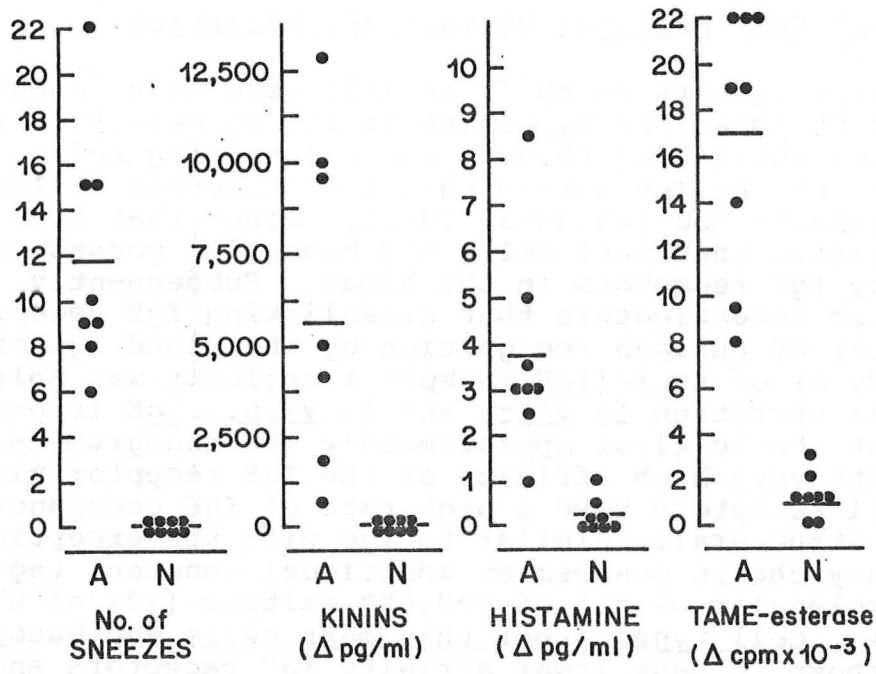
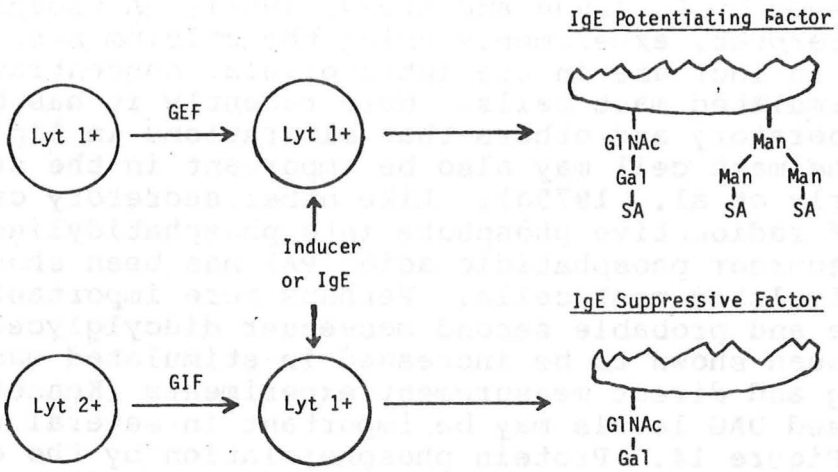


Figure 12

The technique of nasal challenge has provided not only direct demonstration of inflammatory mediators in nasal secretions, but has recently suggested a possible explanation of the biphasic nasal response seen in some patients after allergen challenge. PGD_2 is not seen in the late phase (Naclerior et al., 1984) and since basophils do not synthesize PGD_2, basophil secretion may be responsible for the observed late phase reaction. In addition, intranasal antigen challenge provides an excellent opportunity to study the effect of topical and systemic medications on the production and release of all or specific mediators in nasal secretions.

Mechanisms of Mast Cell Mediator Release and Formation

Although investigators as early as 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 the structure of IgE became known (Ishizaka and Ishizaka, 1967). Since that time it has been demonstrated that mast cells and basophils possess all the high affinity IgE receptors in the human. Subsequently , it was shown by these investigators that crosslinking IgE receptors as a result either of antigen recognition by the bound IgE of anti-IgE antibody or of anti-(IgE receptor) antibody was able to trigger mast cell secretion *in vitro* and *in vivo*. 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). Cell types other than mast cells and basophils that have been shown to have lower affinity IgE receptors and include T and B lymphocytes responsibile for the regulation of IgE synthesis and certain macrophages (reviewed by Geha, 1984). Work in the last 5 years has added tremendously to our knowledge of the regulation of IgE synthesis. In brief and illustrated in Figure 13, a subset of T cells secretes proteins capable of binding IgE termed IgE binding factors. When exposed to antigens using appropriate adjuvants (such as alum), enhancer T cell subsets produce a low molecular weight factor that enhances the glycosylation of IgE binding factors prior to their release (glycosylation enhancing factor). Glycosylated IgE binding factor (IgE potentiating factor) is able to dramatically enhance the differentiation of IgE memory cells to IgE producing plasma cells. In contrast, introduction of antigens in more conventional adjuvants such as Complete Freunds stimulates suppressor T cell subsets to produce a low molecular weight factor (glycosylation inhibitory factor) that reduces the glycosylation of IgE binding factors that supresses the conversion of IgE memory B cells to IgE plasma cells (IgE suppressive factor). Thus, exposure to an allergen in the appropriate form not only produces an increase in specific IgE antibody but also results in a polyclonal enhancement of IgE synthesis. This finding is consistent with the observation that in some atopic states IgE levels are dramatically increased, but usually little is antigen specific (Ishizaka, 1985 and Geha, 1984).



GEF = glycosylation enhancing factor (protease)
GIF = glycosylation inhibitory factor (? lipomodulin/macrocortin)

Figure 13

Other immune mechanisms cause mast cell mediator release. Complement activation (either by the nonspecific alternative pathway or by the specific antibody-mediated classical pathway) results in the formation of anaphylatoxins C3a, C4a, and C5a. C3a and C5a are potent secretory agonists in in vitro model systems of mast cell mediator release. Activation of complement in viral, bacterial, or certain autoimmune diseases may result in physiologically significant mast cell activation although this would not be considered an "allergic" mechanism.

A host of other agents are able to cause mast cell mediator release and include bradykinin, gastrin, a high molecular weight protein from neutrophils and ATP. Recently nasal challenge with methacholine has been shown to cause histamine release into nasal secretions suggesting that neurologic mechanisms may be important in the initiation and/or regulation of mast cell mediator release (Raphael et al., 1985).

A great deal of information has come to light in the last 10 years regarding the biochemistry of mast cell secretion (Schleimer at al., 1984 and Ishizaka et al., 1983). IgE receptor crosslinking results in a rapid and dramatic increase in cyclic AMP levels that return to baseline within one minute of stimulation (Sullivan et al., 1976). Agents that produce a sustained rise in cyclic AMP levels through phosphodiesterase

inhibition inhibit mast cell mediator release (Kennerly et al., 1979c). It has been shown by many groups that there is an early and dramatic increase in calcium permeability and an influx of labeled calcium ions in the mast cell after cross-linking of IgE receptors (reviewed by Sullivan and Brown, 1981). Although more difficult to interpret, experiments using the calcium sensitive dye quin 2 show an increase in the intracellular concentration of free Ca++ in stimulated mast cells. More recently it has been shown by our laboratory and others that alterations in lipid metabolism in the mast cell may also be important in the secretory response (Kennerly et al., 1979a). Like other secretory cells, incorporation of radioactive phosphate into phosphatidylinositol (PI) and its precursor phosphatidic acid (PA) has been shown to be increased in stimulated mast cells. Perhaps more importantly the key intermediate and probable second messenger diacylglycerol (DAG) has also been shown to be increased in stimulated mast cells both in labeling and direct measurement experiments (Kennerly, 1979b). Increased DAG levels may be important in several ways as illustrated in Figure 14. Protein phosphorylation by the enzyme protein kinase C is largely dependent on the presence of DAG and Ca++ (Takai et al., 1981). Also of interest is the observation that DAG is likely an important source of arachidonic acid release by the sequential action of diacylglycerol lipase followed by 2-monoacylglycerol lipase (Kennerly et al., 1979b). This mechanism in the mast cell can release enough arachidonate from DAG in 15 seconds to produce all the newly synthesized lipid mediators seen in mast cell stimulation. It seems reasonable to suspect that at least in the mast cell the combined actions of phospholipase C to produce diacylglycerol and the subsequent lipolytic enzymes diacylglycerol- and monoacylglycerol-lipase may be of greater quantitative importance than phospholipase A2 in the generation of the free arachidonic acid necessary for prostaglandin and leukotriene formation.

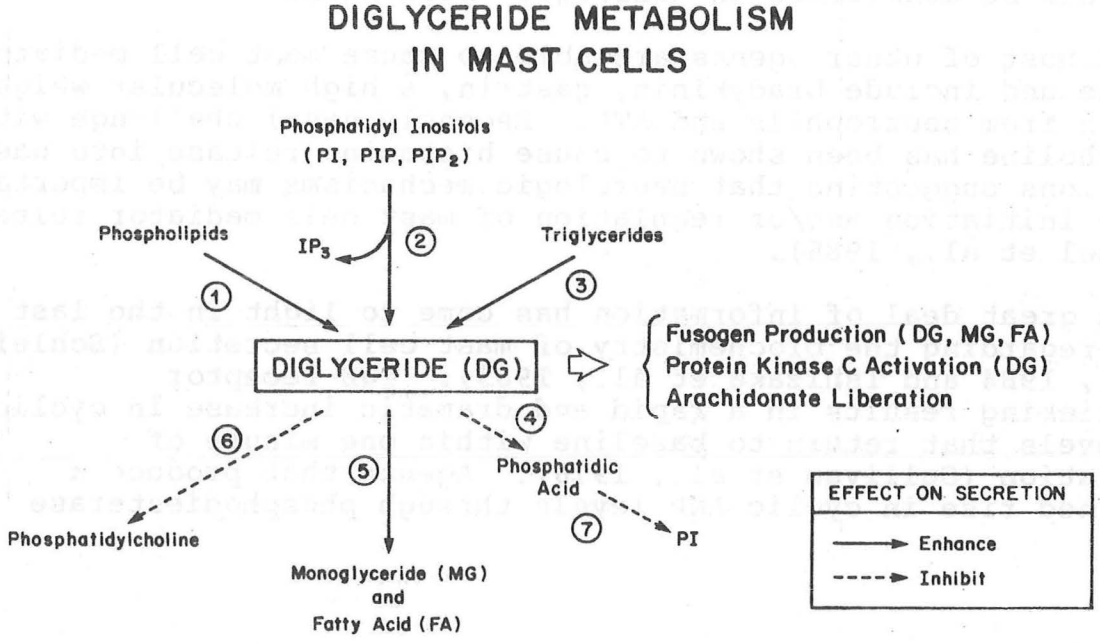


Figure 14

Major Allergens in Allergic Rhinitis

Figure 15 shows that there are 4 major classes of allergens introduced onto the nasal mucous membranes during respiration outside of occupational exposures. As illustrated in Figure 4, important allergens range in size from 5-100 microns in diameter. Particles larger than 100 microns can travel only a relatively short distance in the atmosphere because their high weight to area ratio causes rapid settling. Particles smaller than 5 microns are less effectively adsorbed onto the surface of the nasal mucosa and pass largely unobstructed into the lower airway. Figure 3 demonstrates the pattern of deposition of particles of varying aerodynamic diameter. Recent interesting and provocative studies demonstrate that not all 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 sexually reproduce by pollination utilizing two major mechanisms. In the majority of flowering plants pollination is mediated by insect transfer of pollen grains. For many trees, grasses, and weeds pollination is accomplished by the production of large amounts of pollen that are transfered by air currents. It is very 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 air borne pollination predominate and therefore cause the majority of pollen-induced allergic disease (Solomon, 1984 a&b). Figure 16 presents the major pollens in the Dallas/Ft. Worth area and the times that they are present. Unlike many parts of the country, plant pollens are found in the air in Dallas during the entire year. Shortly after the cessation of Mountain Cedar pollination in late winter, tree pollens emerge followed rapidly by spring grass pollination which extends throughout the summer and overlaps with the summer and fall pollinating weeds. After the first frost there is little pollen in the air until the emergence of Mt. Cedar, usually in December. It is therefore not surprising that

MAJOR NONINDUSTRIAL AEROALLERGENS

Pollens

Mold Spores

House Dust

Animal Danders

Figure 15

many patients in the Dallas/Ft. Worth metroplex with pollen-induced allergic rhinitis have little or no seasonal pattern of exacerbation of their symptoms.

Mold spores are smaller than most plant pollens and are not as important as pollens as the source of allergic rhinitis in this area. Mold spores are produced primarily during humid times of the year by several important genus including Alternaria, Homodendrum, and Helminthsporum.

Plant Pollen In D/FW

		Pollenation
Grasses	Bermuda	Spring-Fall
	Timothy	Spring-Fall
	Red Top	Spring-Fall
	not St. Augustine	
Weeds	Ragweed	Late Summer
	Marsh Elder	Fall
	Russian Thistle	Fall
	Sage	Fall
Trees	Oak	Spring
	Elm	Spring
	Cottonwood	Spring
	Ash	Spring
	Mt. Cedar	Winter

Figure 16

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 a microscopic arthropod, the house dust mite (Dermatophagoides), is the antigen responsible for much house dust sensitivity. House dust tends to collect in mattresses, pillows, carpeting, stuffed furniture, and heavy curtains. Although house dust is present throughout the year there seems to be an increase in symptoms during the heating and cooling seasons, perhaps as a result of increased air circulation during these times and reduced replacement of indoor air by "dust free" outside air. A popular misconception is that dust from dirt roads or construction projects cause IgE-mediated symptoms in house dust sensitive patients.

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. After drying, very small aerosols of these proteinatious compounds are released into the atmosphere of the home and can produce significant perennial or episodic allergic disease.

CLINICAL FEATURES OF ALLERGIC RHINITIS

Definition

A chronic or seasonally relapsing disorder

- Characterized by the presence of nonpurulent rhinorrhea frequently associated with nasal congestion, sneezing, and pruritis of the nose and eyes.

- Induced exposure to aeroallergens that provoke a Type I (IgE-mediated) immune reaction in the nasal mucosa.

Patient History

Important historical features in allergic rhinitis are listed in Figure 17 and include the production of nonpurulent clear nasal secretions that are usually watery. Allergic rhinitis may present at any age but is most commonly encountered in 10 to 40 year old individuals. Figure 1 shows the incidence of allergic rhinitis in Americans by age. It is uncommon for children less than 2 years old to have allergic rhinitis as it seems important to have at least 2 seasons of pollen exposure to develop pollen-induced rhinitis. Younger children seem more frequently to manifest mold spore related allergic rhinitis.

PATIENT HISTORY

- Clear vs purulent nasal secretion
- Seasonal changes
- Environmental alterations
  - workday/weekend
  - inside/outside
  - daily pattern
  - travel
- Pets
- Associated disorders
  - occular pruritis/epiphora
  - sinus headache/infection
  - asthma
- ASA sensitivity/polyps
- Atopic family history

Figure 17

Important symptoms to elicit historically include sneezing, nasal pruritus, congestion, post nasal drip, sinus headache and the presence of concurrent asthma or conjunctivitis. The latter is particularly important in that nearly all patients with rhinorrhea and conjunctivitis have this disorder based upon an IgE-mediated process. It is unusual for patients suffering from both cutaneous and conjunctival atopic dermatitis to additionally have concurrent nonallergic rhinorrhea.

Allergic rhinitis may be seasonal or perennial although the latter often has seasonal exacerbations. The clinical history can give clues as 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. Improvement at work correlates with the decreased dust presence in air as a result of more effective industrial air filtration and shorter pile or absent carpets. Alternatively, slow improvement of symptoms during the work day and exacerbation on the home bound commute and during the weekend especially on outings suggest a pollen as the etiology. A detailed description of the home environment is useful including the duration of living in the Dallas/Ft. Worth metroplex; the presence of wall to wall carpeting, pets, central heating and air conditioning, and humidifiers; and the type of work environment. Response to over the counter antihistamine preparations, nasal sprays or prescription medications is sometimes useful. Rhinitis that improves as a result of antihistamines is more likely to be allergic. 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, childhood atopic dermatitis, urticaria, anaphylaxis or familial history of these disorders is useful as the atopic tendency is inherited in an autosomal dominant fashion with variable penetrance.

Physical Examination

Examining the nose, eyes, and sinuses is particularly important in patients with nasal obstruction and/or rhinorrhea. A summary of relevant physical findings is shown in Figure 18. Nasal exam reveals enlarged edematous and frequently (approximately 50%) pale pink to pale blue nasal mucosa with increased clear nasal discharge. Since the lateral width of the nasal passages is quite variable from patient to patient the observation of nasal obstruction is quite variable in patients with allergic rhinitis. The nasal exam should describe the color and degree of edema of the nasal mucosa as well as the quantity and quality of nasal discharge and the presence of obstruction.

PHYSICAL FINDINGS

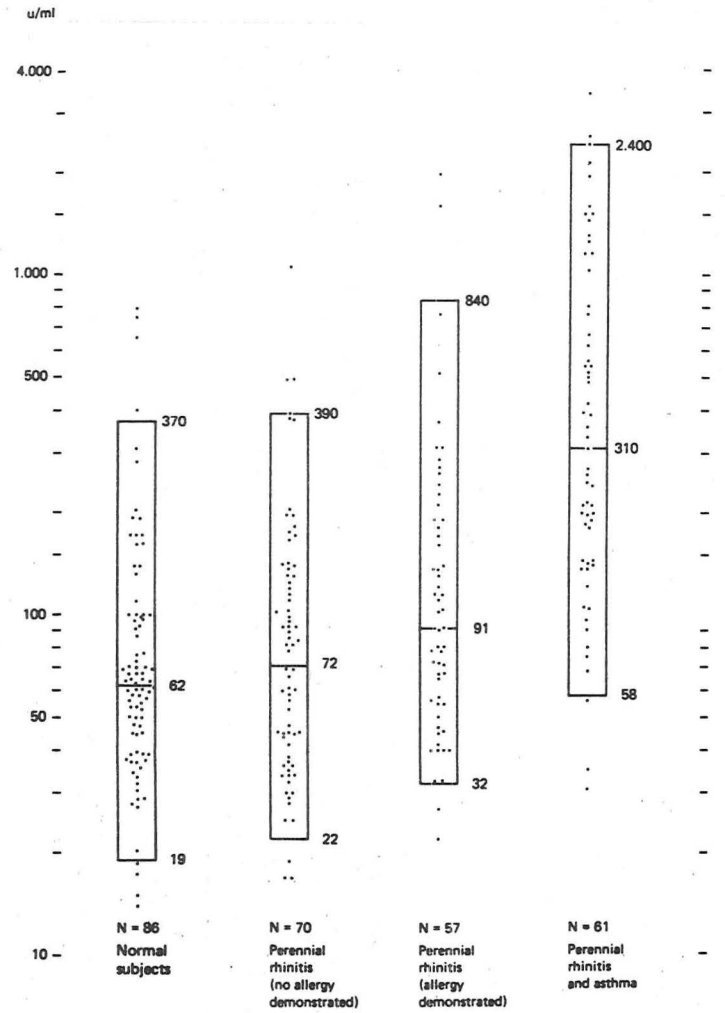
Facial:	Allergic crease Allergic shiners Oral breathing Sinus tenderness
Nasal:	Mucosal edema Mucosal pallor Obstruction Secretions - quantity - color Polyps
Eyes:	Conjunctival vascularity Conjunctival edema
Ear:	SOM
Pharyngeal:	high arched palate/overbite PND

Figure 18

The presence or absence of nasal polyps should be noted. Occular exam for the presence of increased vascularity of the palpebral and/or bulbar conjunctiva is very useful. Transillumination of the sinus and 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 crease at the intersection of the cartilagenous and bony part of the nose ("nasal crease"), the presence of significant overbite and high arched palate from oral airway breathing 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.

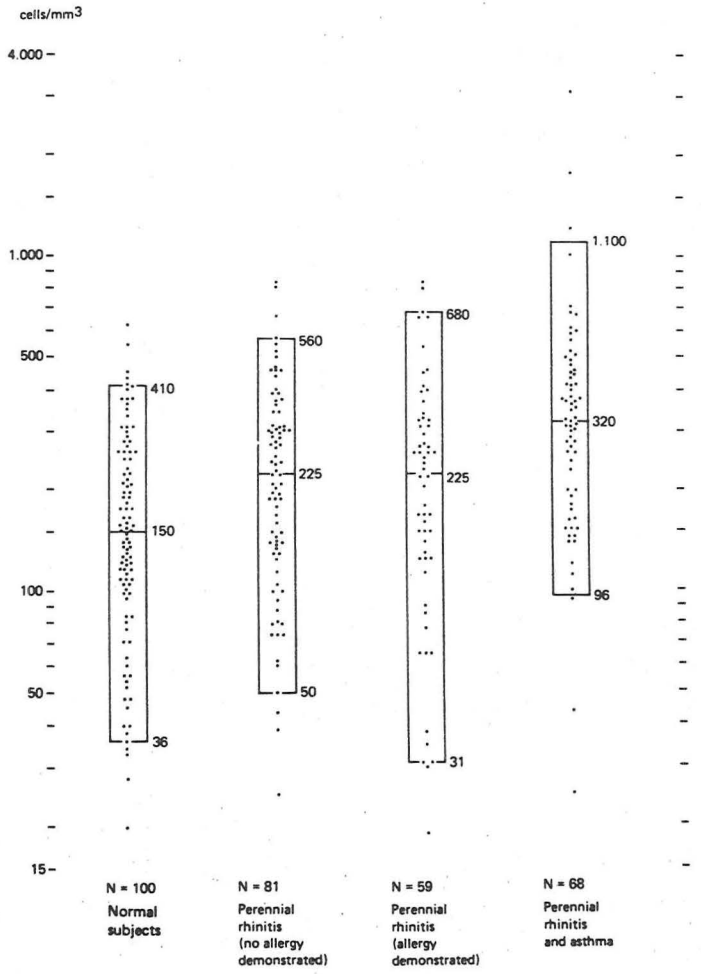
Laboratory Studies

The laboratory investigation of suspected allergic rhinitis is relatively straight forward. As shown in Figure 19, 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 useful only when elevated as a confirmatory finding (Mygind et al., 1978). Circulating eosinophils are similarly of little value in the diagnosis of allergic rhinitis as is illustrated in Figure 20 (Mygind et al., 1978). Sinus radiographs or CT examination may be useful in patients with symptoms of chronic sinus disease.



Serum IgE values in normal subjects and in different groups of rhinitis patients. Five per cent, 50 per cent (median) and 95 per cent percentiles are stated. From Mygind *et al.* (1978).

Figure 19



Blood eosinophil counts in normal subjects and in different groups of rhinitis patients. Five per cent, 50 per cent (median) and 95 per cent percentiles are stated. From Mygind *et al.* (1977).

Figure 20

The most important laboratory finding is almost always overlooked by nonspecialists. A simple Wright stain of the nasal secretions which can be performed in less than 5 minutes in the office and provides a great deal of diagnostically useful information. This can be accomplished by obtaining nasal secretions by either having the patient blow his nose into Saran Wrap or wax paper or removing a small amount of material from the turbinate using a disposable Rhinoprobe™ (RhinoTechnics). Staining takes approximately 1 minute and after drying, microscopic evaluation can yield important information. The presence of eosinophils in the nasal secretions makes the diagnosis of allergic rhinitis quite likely although their absence does not necessarily rule out allergy. Multiple noneosinophil containing nasal smears during periods of symptomatic rhinorrhea make the diagnosis of allergic rhinitis much less likely. A history of topical nasal steroids use must be sought because these agents will often eliminate detectable nasal eosinophilia. The presence of neutrophils and desquamated epithelial cells is seen in viral upper respiratory tract infection.

The demonstration of antigen specific IgE in patients with suspected allergic rhinitis may be of important diagnostic and therapeutic utility but needn't be sought in every patient. The presence of IgE antibodies with important can be determined by prick and/or intradermal skin testing or by RAST testing (reviewed by Nelson, 1983). The former is less costly and gives results rapidly but most internist have little experience in this technique and allergy referral can be costly. Manual prick testing or the use of multiple testing devices is inexpensive, reproducable and reliable. A battery of perhaps as few as 10 antigens would be sufficient for a screening evaluation of patients suspected of having allergic rhinitis, including appropriate saline and histamine controls. The RAST is useful in patients with a generalized dermatitis, concurrent antihistamine use, dermographism, when a life-threatening reaction is feared or in children who are uncooperative.

The demonstration of antigen specific IgE in patients with clear cut seasonal rhinitis is useful primarily when medications have been unsuccessful in adequately treating symptoms and a course of immunotherapy is being considered. In patients with perennial allergic rhinitis, skin testing is useful in discriminating perennial nonallergic rhinitis and the NARE syndrome from perennial allergic rhinitis. The results of skin testing may also be useful from a prognostic standpoint as suggested by the results of a study performed on assymptomatic college students that demonstrated that individuals with intensely positive skin tests had a much higher frequency of developing allergic rhinitis or asthma during the next 7 years (Hagy and Settipane, 1971). Skin testing in the absence of disease while

being of some predicitive utility is not recommended except in unusual circumstances.

DIFFERENTIAL DIAGNOSIS

Obstruction

The differential diagnostic considerations of nasal obstruction are described in Figure 21. The more commonly occurring of these include pregnancy, septal abnormalities, polyps, increased adenoidal tissue, and hypothyroidism while the remainder are relatively uncommon. It is important to distinguish between the presence or absence of rhinorrhea in patients with obstruction. This distinction is not always straightforward, because while anterior nasal discharge is obvious to nearly all patients many complain of nasal obstruction with associated cough or sore throat but are unable to give a clear history of posterior nasal discharge.

DIFFERENTIAL DIAGNOSIS - 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 21

Rhinitis

The differential diagnosis of rhinitis is classified as illustrated in Figure 22. Grossly purulent rhinitis takes place in upper respiratory tract infection complicated by bacterial overgrowth and in rhinosinusitis or polyps with infection.

DIFFERENTIAL DIAGNOSIS - RHINORRHEA

Purulent
- Bacterial rhinosinusitis
- Wegener's gruanlomatosis
- Kartageners syndrome
- Cystic fibrosis

Nonpurulent
- Acute
  - CSF leak
  - irritant exposure
  - viral URI
- Chronic (seasonal) = allergic rhinitis
- Chronic (perennial)
  - With nasal eosinophilia
    - allergic rhinitis
    - nonallergic rhinitis with eosiniphiliq (NARE)
  - Without nasal eosinophilia = vasomotor rhinitis

Figure 22

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 rhinitis can be subdivided into perennial and seasonal categories. Seasonal rhinorrhea is almost always allergic in nature while non-seasonal perennial rhinitis may either be a result of alteration in the normal neurovascular tone and/or response to irritant stimulation (vasomotor rhinitis) or may be allergic in nature either as a result of multiple pollen sensitivities that span the year or to allergenic materials such as housedust and animal danders that have modest seasonal variation. In perennial rhinitis it is particularly important to perform cytologic evaluation of the nasal secretions because perennial rhinitis can be subdivided into three major disorders based largely on the findings of the nasal smear (Figure 22). Repeatedly noneosinophil containing secretions in the absence of positive skin tests results in the diagnosis of nonallergic perennial rhinitis (vasomotor rhinitis). 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). Nonallergic rhinitis with eosinophilia (NARE) is a diagnosis largely of exclusion derived as a result of the failure to find an adequate allergen sensitivity by skin testing and/or RAST that could account for the patient's symptoms. A summary of clinical features of the three types of perennial rhinitis is given in Figure 23 because it is this distinction that is most difficult.

DIAGNOSIS OF PERENNIAL RHINITIS

Parameter	Disease PAR	NARE	VMR
History			
Sneezing	+++	+/-	+/-
Nasal pruritis	++	+/-	-
Rhinorrhea	+++	+++	+++
Physical Exam			
Secretions	watery	mucoid	watery
Polyps	+/-	++	-
Edema	++	+++	++
Laboratory Findings			
Nasal Smear	EOS	EOS	Few PMN
Skin Tests	++	-	-
Associations			
ASA sensitivity	-	+	-
Asthma	++	++	-
Sinus Disease	+	+++	+/-
Response to Tx			
Antihistamines	++	+	-
Steroids	++	++	-
Cromolyn	++	-	-
Decongestants	+/-	+/-	-

PAR = Perennial Allergic Rhinitis
NARE = Nonallergic perennial Rhinitis with Eosinophilia
VMR = Vasomotor Rhinitis

Figure 23

The preceeding discussion has emphasized clinical descriptions that are "classic". In reality patients will often manifest combinations of these three disorders with an emphasis toward 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 having primarily vasomotor rhinitis but with a significant but modest allergic component and a modest response to antihistamines and/or topical nasal steroids would be expected. Thus, these disorders define the clinical spectrum of perennial rhinitis that help to guide our therapeutic decisions.

Diagnostic and Therapeutic value of the Nasal Smear. The presence of eosinophils in nasal secretions should direct the physician either toward the use of pharmacologic agents appropriate to the presumptive diagnosis of allergic rhinitis or toward allergic evaluation in an effort to assess the antigenic cause, if any, of the eosinophilic nasal discharge. The finding of eosinophilia is important from a therapeutic perspective in that patients with either perennial allergic rhinitis or the NARE symdrome (both of which have nasal eosinophilia) respond to topical steroids in a favorable manner. The absence of nasal eosinophilia on a single examination however, is not sufficient to lead the physician to the diagnosis of vasomotor rhinitis. At times when the patient may be less symptomatic an atopic individual may have markedly diminished if not absent nasal eosinophilia. It is crucial to be aware of nasal steroid use because eosinophilia is markedly reduced or eliminated with this therapy. It is suggested that the physician obtain three or more negative nasal smears over a period of several months during times when the disease is active prior to arriving at the diagnosis of vasomotor rhinitis .

THERAPY OF ALLERGIC RHINITIS

General Measures - Avoidance

Once the diagnosis of perennial or seasonal allergic rhinitis is made therapy can be initiated using a variety of approaches. While avoidance remains the optimum mode of therapy it is not practical for the vast majority of patients. Significant pollen reduction in the home is unrealistic despite claims by storm window and filter salesmen. Patients are, however, able to markedly reduce their exposure to animal danders by removing the pets to which they are sensitive from their home environment or at least from their bedroom. It is possible to modestly diminish the presence of house dust through the environmental measures described in Figure 24. Chemicals termed aracacides have been developed that can selectively injure or kill the house dust mite (Mitchell et al., 1985). In addition to the avoidance of materials that provoke specific Ige-mediated reactions it is useful for patients with allergic rhinitis to avoid situations that result in physical, chemical or thermal irritation of the nasal mucosa because these individuals are more sensitive to these nonspecific stimuli. It should be stressed that moving to a different geographic region does <u>not</u> provide a long lasting benefit because patients with allergic rhinitis will usually become sensitized to the pollens or perennial antigens in the new environment.

HOUSE DUST REDUCTION

- Remove carpeting or use removeable short-pile synthetic
- Replace heavy curtains with blinds
- Occlusive matress cover
- Frequent laundering of bed linens
- Replace stuffed furniture with wood or plastic
- Frequent vacuum cleaning and damp dusting
- change heating/cooling system filters
- humidity of 30% - 50%

Figure 24

Medication

Should allergen or irritant avoidance be impractical or ineffective, as it usually is, pharmacologic therapy should be undertaken. Figure 25 illustrates a summary of the approaches that have utility in either reducing mediator release or blocking the ability of inflammatory mediators to cause the symptoms of allergic rhinitis. Therapies that can prevent mast cell mediator release include specific immunotherapy, topical cromolyn sodium, topical or systemic glucocorticoids and certain antihistamines. A second major class of medications block the formation of important mediators of immediate hypersensitivity such as histamine, (by histidine decarboxylase inhibitors) and PGD_2 (by cyclooxygenase inhibitors and steroids). The third class of currently available medications include those that block the effect of released mediators on their targets. The most notable of these agents are the H_1 antihistamines but in addition topical anticholinergic drugs will soon be available in the US that effectively block parasympathetic reflex rhinorrhea. Decongestant medications (primarily alpha sympathomimetic agonists) are able to cause vasoconstriction of both resistance and capacitance vessels resulting in decreased in nasal congestion.

ALLERGIC RHINITIS - TREATMENT

- General Measures
  - Antigen avoidance
    - Pets
    - House Dust
    - Mold Spore (indoor)
  - Irritant avoidance
- Medication
  - Antihistamines
  - Corticosteroids (systemic and topical)
  - Cromolyn sodium
  - Decongestants (systemic and topical)
  - Nonsteroidal antinflammatory agents
  - Topical Anticholinergics
- Immune Modulation (desensitization)
  - Parenteral administration (SQ)
    - aqueous antigen extracts
    - polymerized antigens
  - Nasal administration

Figure 25

Antihistamines - Six classes of H_1 antihistamines are currently available and are well reviewed by Goodman & Gilman but a summary of useful information is presented in Figure 26.

H_1 ANTIHISTAMINES

Class	Prototype	Dosage (mg)	Side Effects			Comments
			Anticholinergic	GI	Sedation	
Ethanolamines	Diphenhydramine (Benadryl)	25-50 q 4-6 hrs	++	-	++	
Ethylenediamines	Pyrilamine (Triaminic)	25-50 q 4-6 hrs	-	++	+	
Alkylamines	Chlorpheniramine (Chlor-trimeton)	4-6 q 4-6 hr (or long acting preps)	-	-	+	
Piperazines	Hydroxyzine (Atarax)	10-25 q 6-8 hr	+	-	++	
Tricyclics	Promethazine (Phenergan)	12.5-25 q 6-8 hr	+	-	++	
	Cyproheptadine (Periactin)	4 q 4-6-8 hr	+/-	+/-	+	Serotonin antagonism
	Doxepin (Sinequan)	2.5-10 q D-BID	-	-	+	
	Azatadine	Not Released	+/-	+/-	+	Inhibits mediator release
"Nonsedating"	Astemizole	Not Released	-	-	+/-	Long acting

Substitution of side chain moieties can drastically alter the degree of antihistaminic effect as well as the type of side effect that is produced by each class of H_1 antihistamine. Considering that local concentrations of histamine likely occasionally exceed 1 mM and frequently exceed 0.1 mM it is not surprising that H_1 antihistamines are often unable to significantly eliminate the symptoms of those suffering from moderate to severe allergic rhinitis. The relatively new antihistamines azelastine azatatline and ketotifen are able both *in vivo* and *in vitro* to not only prevent histamine's effect on end organ tissues but to block mediator release from sensitized mast cells (Fields et al., 1984). Recently several antihistamines have been formulated that poorly cross the blood brain barrier (astemizole) and thus cause less sedation (Nair et al., 1985). These "nonsedating" antihistamines should become available in the next 6-12 months pending FDA approval. 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 - Chromolyn sodium has been used for many years in the treatment of bronchial asthma (Pepys et al., 1974). It has more recently become available in a form for topical nasal use (Nasalcrom). Figure 27 demonstrates the effect of nasal cromolyn treatment on the evolution of an immediate hypersensitivity response in a pollen sensitive individual (Peilkan and Peilkan-Filipek, 1982). Nasal airway resistance

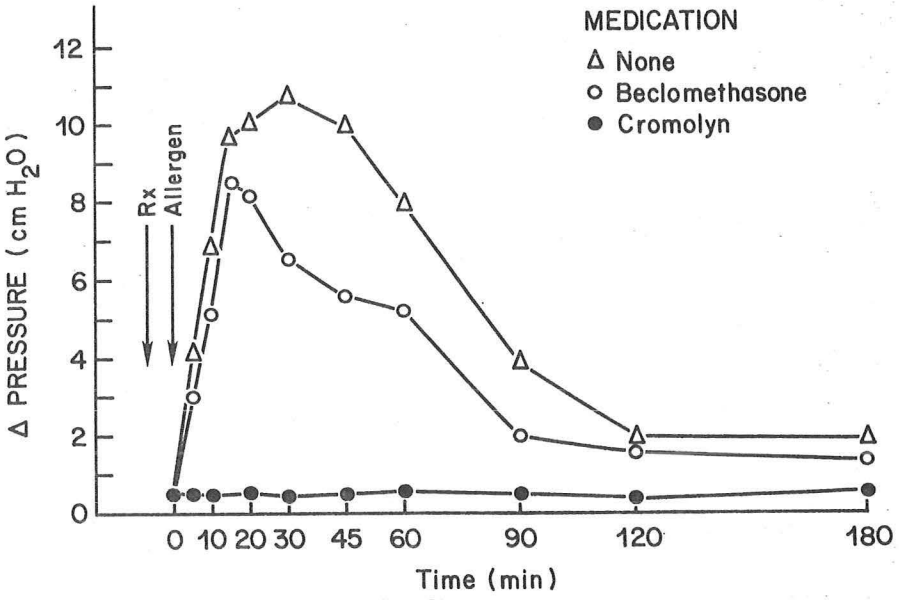


Figure 27

markedly increases after allergen challenge when pre-treated acutely (single dose) either with placebo or topical steroids but cromolyn sodium was able to entirely oblate this response. Nasal cromolyn 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).

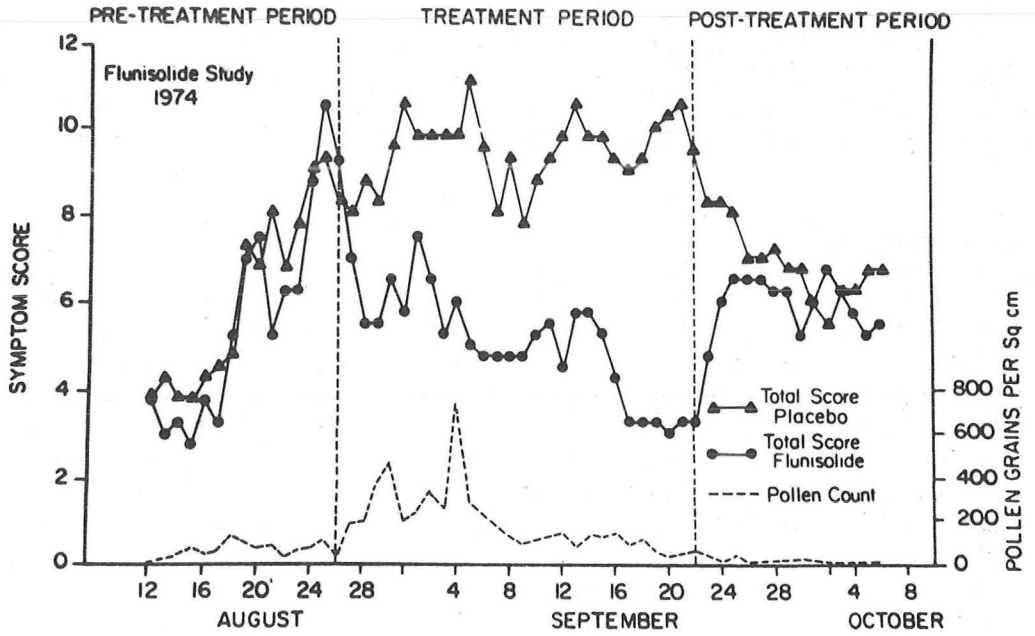
Topical Glucocorticoids - Figure 28 lists the the products of greatest clinical usefulness in the United States today. As illustrated in Figures 29-31, topical steroid preparations are effective in reducing symptoms of seasonal allergic rhinitis, perennial allergic rhinitis, the NARE syndrome and chronic nasal polyposis (Turkeltaub et al., 1982; Tarlo et al., 1977; and Mygind et al., 1975). Long term treatment studies reveal that chronic administration of topical nasal steroids of up to 5 to 10 years does not result in atrophy of nasal mucosa and is without significant side effects (Norman, 1983). These preparations are safe and effective if used at conventional doses. The dose necessary to cause significant reduction in adrenal corticoidsteroid formation is quite high (beclomethasone requires doses at least 3-6 fold greater than the maximum recommended dose) (Harris et al., 1974). While some people complain of mild transient local irritation, this side effect seems to be less prominent in beclomethasone preparations than with flunisolide treatment. Because these preparations often require 1-2 weeks of TID use prior to significant symptom relief, patients should be alterted to this lag in an attempt to improve compliance.

INTRANASAL CORTICOSTEROIDS

Product	Delivered Dose (ug)	Delivery System	Recommended Dosage[1]	Disadvantages
Dexamethasone (Turbinaire-Merck)	100	Freon	2 puffs TID	Adrenal Suppression
Beclomethasone (Beconase-Galaxo) (Vancenase-Schering)	42	Freon	1 puff BID-QID	
Flunisolide (Nasalide-Syntex)	25	Pump	2 puffs BID	Local Irritation

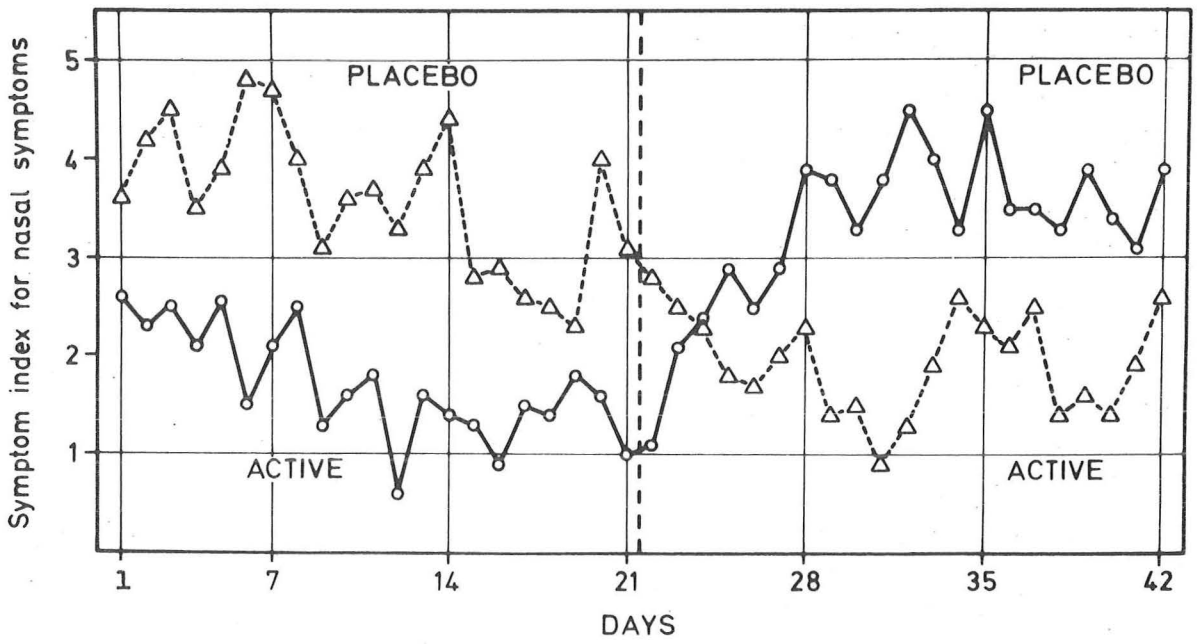
[1] = Dosage is per nostril

Figure 28



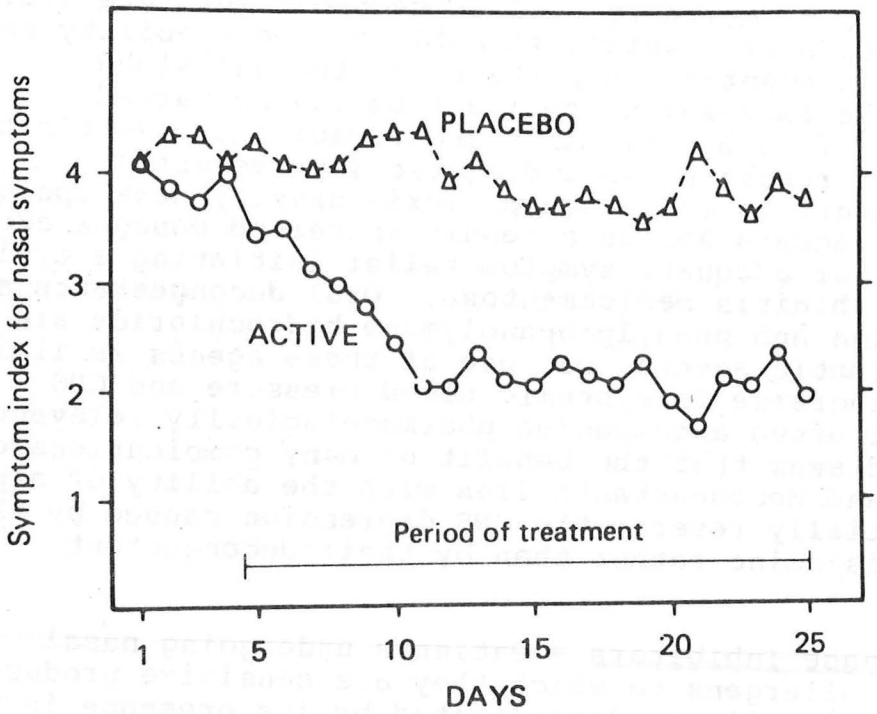
Average daily symptom scores of each treatment group and the daily ragweed pollen count. (From Turkeltaub PC et al: J ALLERGY CLIN IMMUNOL 58:597, 1976.)

Figure 29



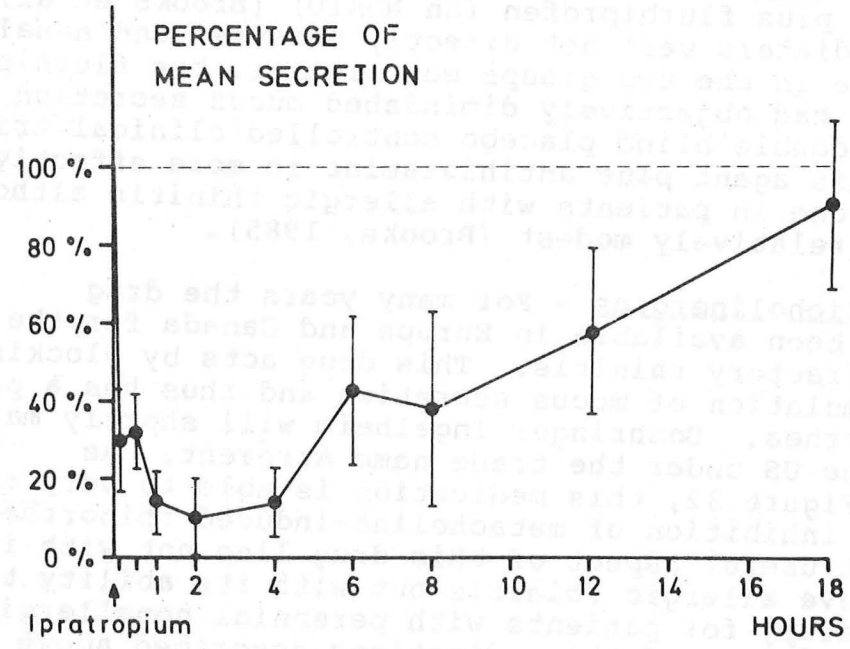
Average daily symptom scores of perennial rhinitis in adults treated with beclomethasone dipropionate. From Hansen and Mygind (1974).

Figure 30



Average daily symptom scores for nasal symptoms in patients with nasal polyps, treated with beclomethasone dipropionate. From Mygind *et al.* (1975).

Figure 31



The nasal secretory response (mean ± SEM) to metacholine at varying time intervals after ipratropium application in 6 subjects. Already 5 minutes after pre-treatment the response was reduced to 30 per cent of the initial value. The effect was significant in the first 8 hours. From Borum (1978b).

Figure 32

Decongestants - Topically applied decongestants are effective in reducing symptoms of allergic rhinitis by their ability to act as sympathomimetic agents. In particular, topical alpha stimulation by the imidazoline derivatives causes marked vasoconstriction of both resistance and capacitance vessels in the nasal vasculature resulting in a dramatic improvement of obstruction. Unfortunately, tachyphylaxis usually develops quite rapidly to these agents and as a result increased dosages are frequently used for adequate symptom relief initiating a cycle that results in rhinitis medicamentosa. Oral decongestants such as pseudoephedrine and phenylpropanolymine hydrochloride are also alpha sympathomimetic agents, but use of these agents is limited because of the increase in systemic blood pressure and CNS stimulation that often accompanies pharmacologically relevant doses. It would seem that the benefit of many combinations of antihistamines and decongestants lies with the ability of alpha agonists to partially reverse the CNS depression caused by the component antihistamine rather than by their decongestant properties.

Cyclooxygenase Inhibitors - Patients undergoing nasal challenge using allergens to which they are sensitive produce prostaglandin D_2 locally as demonstrated by its presence in the nasal secretions (Naclerio et al. 1983). Because PGD_2 may play an important role in the evolution of allergic rhinitis, the inhibition of its synthesis by cyclooxygenase inhibitors (nonsteroidal antiinflammatory drugs or NSAID's) has recently been studied. Patients with pollen-induced allergic rhinitis were challenged either after chlorpheniramine (an H_1 antagonist) or chlorpheniramine plus flurbiprofen (an NSAID) (Brooks et al., 1984). While mediators were not directly measured and nasal airway resistance in the two groups was similar, the flurbiprofen treated patients had objectively diminished mucus secretion and sneezing. In a double blind placebo controlled clinical trial it appeared that this agent plus antihistamine is more effective than antihistamine alone in patients with allergic rhinitis although the effects are relatively modest (Brooks, 1985).

Topical Anticholinergics - For many years the drug ipratropium has been available in Europe and Canada for the treatment of refractory rhinitis. This drug acts by blocking cholinergic stimulation of mucus secretion and thus has a primary impact on rhinorrhea. Boehringer Ingelheim will shortly market this agent in the US under the trade name Atrovent. As illustrated in Figure 32, this medication is able to very rapidly bring about the inhibition of metacholine-induced rhinorrhea. Perhaps the most useful aspect of this drug lies not with its ability to improve allergic rhinitis but with its ability to offer a reasonable therapy for patients with perennial nonallergic rhinitis for which none of the medications described above and below are consistently effective (Borum et al., 1979 and Dolovich

et al., 1985 and Figure 25). In addition, double blind randomized trials in Europe indicate that Atrovent may be a very useful therapy in treating the rhinorrhea of the common cold (Borum et al., 1981).

Systemic glucocorticoids - Systemic glucocorticoids are extremely effective in reversing allergic rhinitis usually after 24-48 hours. The effects of glucocorticoids are clear but the mechanism is less certain. Although high dose steroid treatment has no effect on skin testing, in vitro rodent mast cell mediator release can be reduced by pretreatment with glucocorticoids (Marquardt and Wasserman, 1983). 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 Hirato et al., 1981) has been proposed. The impact of glucocorticoids on nasal PGD_2 and LTC_4 synthesis in nasal challenge remains to be done. Perhaps too much concern is expressed regarding the side effects of systemic glucocortocoids particularly in younger patients with a low probability of latent contraindications. Chronic therapy is of course not recommended for non life threatening allergic diseases and thus asthma remains the only allergic disease for which chronic steroid therapy may be indicated. Episodic systemic glucocorticoid therapy is an important element of the treatment of some patients with allergic seasonal or perennial rhinitis as illustrated in Figure 33. Systemic glucocorticoids are particularly useful in the initiation of therapy in patients with moderate to severe allergic rhinitis. If the nose is significantly obstructed, delivery of topical steroids and/or cromolyn to the nasal mucosa is markedly impaired.

SYSTEMIC CORTICOSTEROID THERAPY

Diagnostic trial

Initiation of topical therapy (steroids or cromolyn)

Episodically for severe symptoms

vs Surgery in nasal polyposis

Rhinitis medicamentosa

Figure 33

In these patients the physician is left with the choice of either using topical decongestant medications, systemic steroids, or accepting the relatively poor and slow response to topical steroids (which often results in poor compliance). The use of

topical decongestants may present the opportunity for abuse in the patient who has not used these agents previously. A course of prednisone (40 mg/day) for 3-5 days is often able to cause markedly reduced nasal obstruction and thereby permit adequate delivery of topical glucocorticoids to the entire nasal mucosa. Topical glucocorticoids often require one to two weeks prior to achieving a maximum benefit so these agents should be started coincident with systemic steroids or topical decongestants. In the patient with rhinitis medicamentosa, systemic glucocorticoid treatment for 5-7 days permits the rapid withdrawal of nasal decongestants without the occurrence of rebound nasal obstruction.

In patients where the allergic basis of rhinitis is uncertain, treatment with systemic steroids maybe of benefit from a diagnostic standpoint because nearly all patients with allergic rhinitis or the NARE syndrome have marked improvement in their symptoms. Patients with perennial non-allergic rhinitis (vasomotor rhinitis) rarely improve.

Novel Drug Therapies - A variety of medications have a theoretical if not practical role in the management of allergic rhinitis.

Crysotherapeutic agents have been used for many years in the therapy of rheumatoid arthritis. A small body of literature is evolving largely in Japan that suggests that patients with asthma may obtain remission while on gold (Araki, 1969 and Maranaka, 1978). Recently *in vitro* models suggest that gold treated animals have a reduced bronchospastic sensitivity to histamine (Yamauchi et al., 1984) and that realistic levels of soluble gold compounds block antigen-induced human basophil mediator release (Takaishi et al., 1984). No data are available regarding gold and allergic rhinitis.

Histamine is synthesized intracellularly by the conversion of histidine to histamine by histidine decarboxylase. A number of compounds block this conversion but a preliminary report suggests that despite the ability of a histidine decarboxylase inhibitor to diminish nasal histamine by 65%, nasal antigen challenge in treated patients was not associated with a reduction of nasal secretion or sneezing (Pipkorn et al., 1985). Skin test reactivity was similarly not affected. More work remains to examine the effectiveness of these and possible more effective inhibitory agents in combination with other classes of therapeutic agents in effecting improvement of allergic rhinitis.

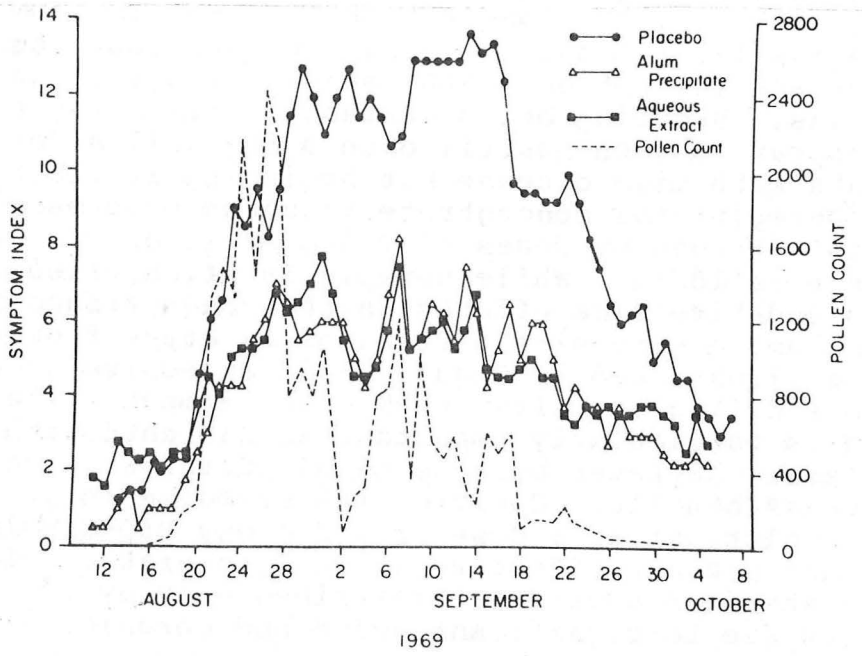
Because theophylline can reduce mast cell secretion (Kennerly et al., 1979c) (although it requires supraphysiologic dosages *in vitro*) it may have a role in allergic rhinitis probably through its effect on adenosine metabolism (Marquardt et al., 1984) but studies determining its effectiveness *in vivo* in allergic rhinitis

are wanting.

Beta adrenergic drugs applied topically to the nasal mucosa have the theoretical advantage of blocking mast cell mediator release, but are hampered by direct albeit mild vasodilation. Anecdotes describe minimal benefit and no studies are available.

Immune Modulation

For nearly 75 years physicians have been introducing allergens into patients in the hopes of improving their allergic disorders. Although the scientific basis of this treatment was incorrect initially and is still poorly understood, multiple double blind placebo controlled randomized studies have shown that parenteral immunotherapy is able to reduce or eliminate the symptoms of both perennial and seasonal allergic rhinitis (Lowell and Franklin, 1963; Lichtenstein et al., 1974; and Ortolani et al., 1984). Studies have shown that the IgG "blocking" antibodies increases as a result of a course of desensitization while the seasonal rise in allergen specific IgE is blunted (Gleich et al., 1982). Conventional immunotherapy usually involves the subcutaneous introduction of aqueous extracts of appropriate antigens in increasing doses over about 30 weekly or semiweekly injections limited by the development of local or systemic reactions. During the ensuing 2-4 years monthly injections of the highest tolerated dose ("maintenance" dose) is maintained. Figure 34 demonstrates the effectiveness of desensitization of patients with ragweed allergic rhinitis in the Baltimore metropolitan area (Lichtenstein et al., 1974).



Average daily symptom scores of ragweed hay fever in patients treated as indicated. Immunotherapy diminished hay fever symptoms by a half. The data also illustrate that treatment with aqueous extract and treatment with alum-precipitated extract (Allpyral®) gave identical degrees of amelioration. From Lichtenstein *et al.* (1974). By courtesy of the author and Excerpta Medica, Amsterdam.

Figure 34

During the last decade certain important pollen antigens have been isolated and polymerized so that fewer doses of this polymerized antigen are required to achieve significant clinical benefit (Grammer et al., 1984). These materials however are still experimental and have been used with few antigens.

A more recent and fascinating approach to therapy involves the preseasonal intranasal administration of increasing doses of aqueous antigen extracts. Patients with seasonal allergic rhinitis are "desensitized" by a one month pre-treatment of increasing doses of aqueous extracts. In limited trials this approach has had documented clinical efficacy (Georgitis et al., 1984). Antigen specific paralysis of mast cell mediator release to the antigens involved likely occurs by an uncertain mechanism probably similar to penicillin desensitization described in detail by Dr. Sullivan at these grand rounds 3 years ago.

As described earlier, the mechanisms that regulate IgE synthesis are becoming better known. It seems likely that before long, glycosylation inhibitory factor may be used in atopic patients to reduce IgE synthesis in an effort to reduce antigen initiated IgE-mediated mast cell mediator release.

Approach to Therapy

In patients with documented seasonal or perennial allergic rhinitis a two pronged attack utilizing antihistamines and topical glucocorticoids is usualy effective. Systemic glucocorticoids may be important in initiating this therapy. If symptoms are adequately controlled with a combination for example of beclomethasone nasal spray and doxepin, patients can frequently reduce or eliminate (except on a PRN basis) the use of one of their medications. Reducing beclomethasone nasal spray to as little as one spray in each nostril once a day will afford relief in many patients with mild disease but beginning at TID is recommended. Doxepin oral concentrate is often used because relief is often afforded by doses of 2.5-5 mg qD or BID, and the smallest capsule is 10 mg. While doxepin is often tried first by our group, its sedative side effects in the nondepressed patient are significant and may require a trial of an agent from a different class illustrated in Figure 26 if excessive sedation does not improve during the first week of treatment. The use of antihistamines is particularly important in patients with occular symptoms in classic hayfever because nasal steroids of course produce no occular benefit. Opticrom (4% cromolyn in ophthalmologic solution) at a dose of 1-2 drops BID-QID is added if antihistamines are not effective or well tolerated. Topical ophthalmologic steroids should be prescribed only by ophthalmologists due to significant acute and chronic complications of their use.

If combined nasal steroids and antihistamines are not adequate in controlling allergic rhinitis the best additional drug to use is topical nasal cromolyn sodium (Nasalcrom) although its effects are not consistent. Nasal decongestants cannot usually be used chronically due to tachyphylaxis and their potential in resulting in rhinitis medicamentosa. Episodic use of nasal decongestants in compliant patients is important in difficult allergic rhinitis. Oral decongestants are of marginal if any additional benefit. In patients with significant allergic conjunctivitis Opticrom not only improves allergic conjunctivitis but because the lacrimal duct drains into the nose, cromolyn solution is delivered to the area below the inferior turbinate of the nose and may benefit the associated rhinitis. For patients who have inadequate benefit with these therepeutic alternatives or for patients who are unable or unwilling to take this degree of chronic medication (particularly for patients with perennial allergic rhinitis) a course of desensitization to offending antigens may be indicated.

Treatment of Nonallergic Rhinitis

Patients with the NARE syndrome usually improve with topical glucocorticoids while antihistamines have a variable role. The prompt treatment of complicating sinus disease or bacterial rhinitis is important in reducing the chronic inflammatory component of non allergic rhinitis with eosinophilia or nasal polyposis.

At present, vasomotor rhinitis is not only poorly understood but is also very poorly treated. The chronic use of vasoconstrictor medications may be of modest benefit if used in a limited fashion (at night to permit sleeping, for example) so that tachyphylaxis does not evolve. The upcoming availability of the topical anticholinergic Atrovent (ipratropium) may well produce marked improvement in these currently inadequately treated patients (Borum et al., 1979 and Dolovich et al., 1985).

COMPLICATIONS OF ALLERGIC RHINITIS

Complications of allergic rhinitis are relatively common but usually not severe. Serus otitis media as a result of eustachian tube obstruction secondary to local allergic inflammation occurs although it is relatively uncommon (Ackerman et al., 1984). Chronic inflammation and edema associated with chronic allergic rhinitis predisposes patients to the development of sinus disease. Lack of sinus drainage not only produces headache but may be complicated by either acute or chronic mild or severe infection that often benefits from antibiotic intervention and the temporary use of decongestant to improve sinus drainage.

Although quite controversial (Schumacher et al., 1985), one potential complication of allergic rhinitis is bronchospasm caused by the so called nasobronchial reflex illustrated in Figure 35.

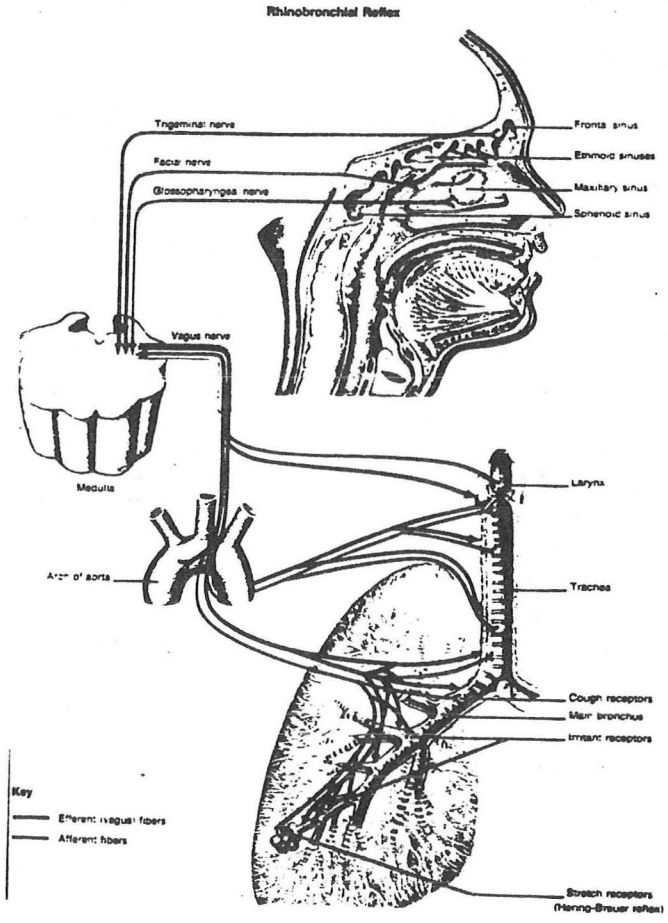


Figure 35

Several studies show that the acute irritation caused by introduction of silica powder only into the nose increases lower airway resistance (Kaufman et al., 1970). Anticholinergic medications seem to block the expression of this finding as does the section of the ipsilateral trigeminal nerve for the symptoms of tic doloureaux (Kaufman and Wright, 1969 and Kaufman et al., 1970). This finding suggests that in patients with allergic rhinitis and asthma (a frequent combination of disorders) attention to treatment of the allergic rhinitis may be of significant importance in improving a patient's pulmonary status. In addition, the chronic cough induced by post nasal drip often exacerbates asthma.

A frequent and troublesome complication of chronic nasal congestion is the loss of smell and the diminution of taste. These are hardly life-threatening, but like much of the morbidity of allergic rhinitis cause a significant reduction in the quality of life.

FUTURE DIRECTIONS

The future is quite bright for the ultimate control of allergic diseases. During the last many millenia it seems likely that the IgE system evolved as a response to adequately protect individuals from excessive parasite burdens. The relatively recent removal of parasites from industrialized societies may have caused this system to search for other musocal antigens with which to react. Despite the presence of astute clinicians in the past, allergic rhinitis has only been described for 150 years suggesting that it is truly of relatively recent vintage. During the last 50 years our clinical and scientific knowledge has expanded nearly as rapidly as the increased incidence of the disorder. The likelihood of developing clinically relevant methods of IgE suppression seem high in the next 10-20 years. In addition, the appearance in the US during the next 6 to 12 months of a topical anticholinergic medication (Atrovent) will improve patients with allergic and nonallergic rhinitis. In addition, new and simpler methods of desensitization are becoming available and the potential of preseasonal rapid desensitization to specific antigens by nasal instillation by aqueous antigen extracts may remove immunotherapy from the physicians office for the intelligent patient.

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