
MECHANISMS OF RHINITIS

James N. Baraniuk, MD

CLASSIFICATION OF RHINITIS

As can be seen by the contents of this issue, the differential diagnosis of rhinitis is large and somewhat complex (Table 1 and Box 1).¹⁸ The patients with rhinitis can be approached by a series of questions: (1) Is this normal or disease? (2) Is it purulent or nonpurulent? (3) Are symptoms seasonal or perennial? (4) Is the inflammation eosinophilic, neutrophilic, or are there no changes in inflammatory leukocytes? (5) Are anatomic factors such as septal spurs or deviated septum the source of complaints?⁴³ This algorithm and the many disorders of the nasal and sinus mucosa reflect the skills of clinicians to identify specific symptom complexes, the accessibility of the nostrils for the collection of nasal cells and secretions (e.g., eosinophilia), the information gained by allergen and other nasal provocation studies, the ability to perform biopsies and make disease-specific tissue diagnoses, and the explosion of information about the molecular biology of nasal and sinus diseases.² As a result, it is possible to discriminate between a large number of infectious, metabolic, vasculitic, drug-induced, atrophic, physical, chemical, and other triggers

Supported by US Public Health Service Award AI42403 and Environmental Protection Agency Award R825814. Although the research described in this article has been funded wholly or in part by the United States Environmental Protection Agency through Grant R825814 to James N. Baraniuk, MD, it has not been subjected to the Agency's required peer and policy review and therefore does not necessarily reflect the views of the Agency and no official endorsement should be inferred.

From the Division of Rheumatology, Immunology, and Allergy, Georgetown University, Washington, DC

IMMUNOLOGY AND ALLERGY CLINICS OF NORTH AMERICA

Table 1. THE SPECTRUM OF RHINITIS

Inflammatory Rhinitis			Noninflammatory Rhinitis	
Eosinophilic	Neutrophilic	Other	Irritant	Other
Allergic rhinitis	Bacterial sinusitis	Viral rhinitis	Vasomotor rhinitis	Hypothyroidism
NARES	Adenoiditis	Wegener's granulomatosis	Irritant rhinitis	β -blocker
Nasal polyps	Cystic fibrosis	Sarcoidosis	Multiple chemical sensitivity	Other vasodilating antihypertensives
Chronic eosinophilic sinusitis syndrome		Midline granuloma	Cholinergic hypersecretory rhinitis	Pregnancy
Aspirin sensitivity		Other unusual inflammatory conditions	Gustatory rhinitis	Chronic fatigue syndrome
			Skiier's nose	Tumor
				Atrophic rhinitis

NARES = nonallergic rhinitis-eosinophilia syndrome

that can lead to rhinitis symptoms.^{34, 58} Each author's differential diagnosis and algorithm for rhinitis analysis varies slightly.^{2, 18, 34, 43, 58} In this article a slightly different approach has been taken by segregating rhinitic disorders into those characterized by: (1) cellular inflammation; (2) predominantly irritation, congestion, or rhinorrhea symptoms without obvious physical changes; and, (3) conditions related to hormonal and other treatments (Table 1). A more traditional approach expanding and defining some of these categories also is reviewed (see Box 1).

A full description of all potential mechanisms contributing to rhinitis is beyond the scope of this article, especially because several of these mechanisms have been dealt with elsewhere in this issue. The basic reductionist approach that the author developed identifies four major compartments in the nasal mucosa that account for the most of the signs and symptoms of rhinitis (Fig. 1). The superficial postcapillary venules are responsible for the endothelium-directed leakage of plasma that leads to local edema and watery rhinorrhea. These endothelial cells direct leukocyte traffic by the expression of chemoattractants and adhesion markers that recruit the unique sets of interstitial, epithelial, and luminal cellular inflammation in various forms of rhinitis. The deep venous sinusoids control nasal patency on the minute-to-minute schedule and longer nasal cycle schedule. These vasomotor processes are orchestrated by brain stem rhythms and enacted by way of autonomic nerves. Finally, the epithelial and glandular serous and mucous cells contribute the sol phase antimicrobial defense factors (e.g., secretory

Box 1. Differential Diagnosis of Allergic Rhinitis

- Allergic Rhinitis
 - Perennial: usually indoors (e.g., dust mites, dogs, cats, cockroaches, molds)
 - Seasonal
 - Antigen-specific (e.g., shrimp fumes, librarians, and book molds)
- Infectious Rhinitis
 - Viral
 - Bacterial rhinosinusitis
 - Fungal rhinosinusitis
- Nonallergic Rhinitis
 - Nonallergic rhinitis with eosinophilia syndrome (NARES)
 - Vasomotor rhinitis: daily symptoms of nasal congestion, sneezing, discharge, with acute symptoms following exposure to irritant conditions (e.g., fumes, paint, cigarette smoke, pollution, newspaper newsprint, cold air)
 - Wet vasomotor rhinitis: rhinorrhea predominates
 - Dry vasomotor rhinitis: congestion, sneezing predominates
 - irritant rhinitis (a more representative term that describes the perceived link between irritants such as tobacco and nasal discomfort)
 - Nasal polyps
 - Aspirin sensitivity with rhinitis with or without nasal polyps
 - Triad asthma
 - Occupational, toxic reactions: plicatic acid (e.g., western red cedar)
 - Drugs (e.g., cocaine)
 - Rhinitis Medicamentosa
- Ciliary dysmotility with bacterial rhinosinusitis
- Structural deformities impairing sinus drainage
 - Trauma
 - Septal deviation
 - Concha bullosa (i.e., ethmoid air cell in middle meatus)
- Vasculitis
 - Wegener's granulomatosis
 - Midline granuloma
 - Other vasculitic processes

immunoglobulin A [sIgA]), sticky gel phase mucopolysaccharide mucins, and ionic composition of the nasal epithelial lining fluid.^{5, 49}

Several new immunopathologic principles will lead to a restructuring of this differential diagnosis in coming decades as we learn more about: (A) the various subtypes of lymphocytes driving antigen-specific inflammation; (B) differentiation and restructuring of epithelial and other mucosal structures (e.g., sinusitis),¹³ (C) neurogenic mechanisms responsible for irritant syndromes that lack any apparent mucosal inflammation^{7, 8}; and (D) the structure of the human genome. It is already clear that the genes expressed on the distal portion of the long arm of chromosome 5 (5q31.1–q33) play major roles in atopy, vernal keratoconjunctivi-

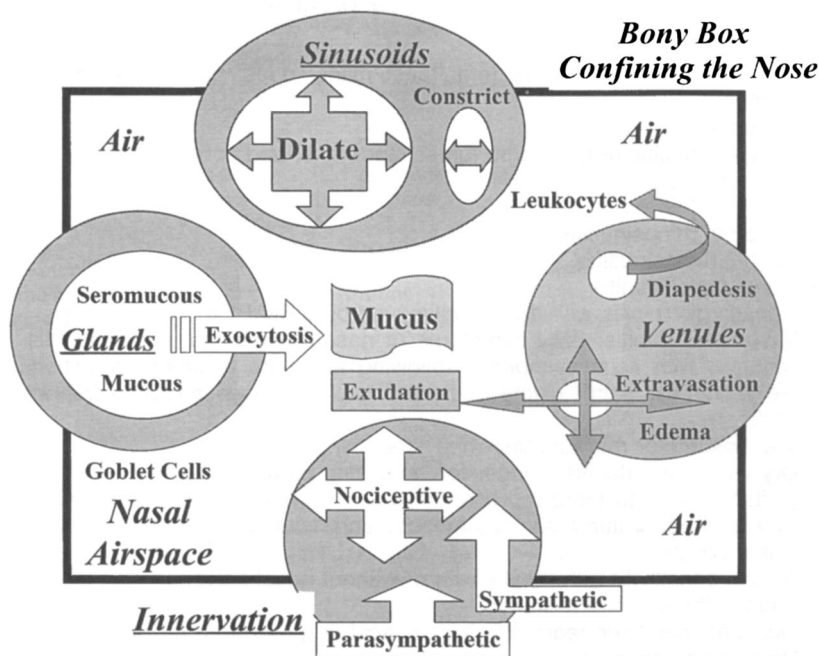


Figure 1. Reductionist view of the nasal mucosa. The four functional components of the nasal mucosa as invaginations into the nasal airspace: (1) The venous sinusoids swell and constrict in response to sympathetic tone and other mechanisms. They serve as the predominant mechanism to regulate nasal air flow and patency. (2) Postcapillary venules are present in the superficial lamina propria, and are the site of plasma extravasation and leukocyte diapedesis. Their endothelial cells respond to a wide range of blood-borne and interstitial mediators by contracting, which opens gaps on the basement membrane. They express adhesion markers and release nitric oxide, endothelin, and other mediators that regulate vascular tone. (3) The exocytosis domain is composed of the surface epithelial goblet; microvilli; and ciliated, glandular seromucous, and mucous cells. Seromucous cells release antimicrobial factors, such as lysozyme, lactoferrin, secretory IgA, hyaluronan, neutral mucins, and other factors. Mucous cells and goblet cells release acidic mucins coated with sialic acid and sulfate groups that make them exceedingly "sticky" and permit them to adsorb any particulate or irritant chemicals that may be present on the mucosal surface. (4) The final domain represents the innervation of these structures. Nonmyelinated type C nociceptive nerves are highly branched in the epithelium. There may be functional subsets mediating sensations of itch (H_1 receptors present) or burning pain (capsaicin-sensitive vanillyl receptor present). Parasympathetic nerves include cholinergic nerves and possibly a separate set of vasoactive intestinal peptide (VIP)-nitric oxide–substance P–containing neurons, as has been shown in ferret trachea. Sympathetic fibers are responsible for vasoconstriction of the venous sinusoids. These fibers contain norepinephrine or norepinephrine plus neuropeptide Y. The predominant norepinephrine effect seems to be the vasoconstriction and collapse of the venous sinusoids, thinning of the mucosa, and an increase in nasal patency. Neuropeptide Y is unique because it can reduce vascular permeability induced, for example, by bradykinin. (Courtesy of J. Baraniuk, MD, Washington, DC.)

tis,¹⁵ myelodysplastic,³⁹ and other neoplastic syndromes (Box 2).^{25, 53} It is also of interest that the β 2-adrenergic, α 1B-adrenergic, dopamine type 1A, and glucocorticoid receptors also are clustered to this region.³⁶

The concept that there are type I T lymphocytes that produce predominantly interferon- γ (IFN- γ) and type II T cells that predominantly secrete interleukin-4 (IL-4) has revolutionized the concepts of lymphocyte function. These type I and type II concepts affect CD4⁺ helper (Fig. 2) and CD8⁺ cytotoxic/suppressor populations (Fig. 3). Further findings in this field will restructure our views of how individual pathogens can lead to seemingly unrelated symptom complexes (e.g., tuberculoid and lepromatous leprosy [Fig. 2]). It is already possible to expand the original Gell and Coombs classification of four basic immune mechanisms¹⁷ by including type I and type II components of CD4⁺ and CD8⁺ cell populations along with the three traditional humoral immune mechanisms and *pseudoallergic* anaphylactoid responses (Table 2).

For the present, the best rationalization for the T_H2 immune response would seem to be as a prototypic antiparasitic mucosal protection mechanism. This hypothesis is useful to explain the IgE-plasma cell, mast cell and eosinophil infiltration, mucous secretion, smooth muscle spasm, extreme vascular permeability, and vasodilation that characterize the immediate, type I hypersensitivity reaction in hollow viscuses, other

Box 2. Genes Expressed Along Human Chromosome 5q31.1–q33

IL-3

Granulocyte-macrophage colony-stimulating factor (GM-CSF)

IL-5

IL-13

IL-4

IL-9

Macrophage colony-stimulating factor (M-CSF)-receptor

IL-12B p40 (40 kDa) monomer

Anonymous gene that may control the maintenance of responsiveness to IL-12

Fibroblast growth factor (FGF-1) (acidic)

Early growth response gene 1 (EGRF-1)

Endothelial cell growth factor

Platelet-derived growth factor

Feline myosarcoma viral oncogene homolog (feline myosarcoma [FMS], tyrosine kinase)

CD14 monocyte differentiation factors

Dopamine receptor type 1A

α 1B-adrenergic receptor

β 2-adrenergic receptor

Glucocorticoid receptor

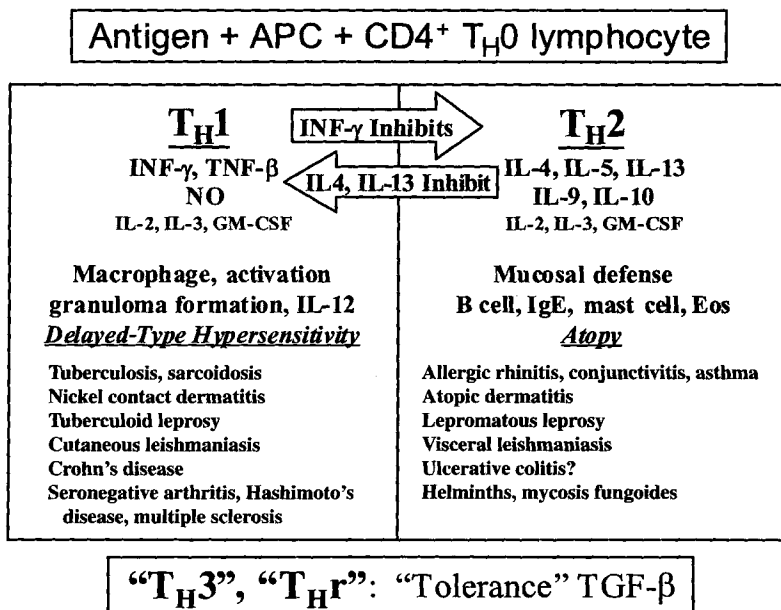


Figure 2. T_H1 versus T_H2 hypothesis. The local cytokine and adhesion marker environment of the antigen, antigen-presenting cell, and naive T-cell (T_H0) interaction determine the future differentiation, function, and cytokine production of T cells. T_H1 cells are responsible for macrophage activation, and cause slow or delayed-type hypersensitivity. T_H2 cells lead to atopy and the IgE-mast cell-mediated type I immediate hypersensitivity. T_H2 cells alone that are not linked to IgE reactions may cause late-phase reaction (LPR)-like cellular reactions that could play a role in asthma and atopic dermatitis. The example of leprosy is instructive because, although only one organism—*Mycobacteria leprae*—is involved, the spectrum of the disease from effective granulomatous tuberculoid leprosy (T_H1) to the ineffective humoral immune responses of lepromatous leprosy (T_H2) is determined by the human host. Other diseases may fit this spectrum. It is not likely that the human population has a bipolar distribution of T_H1- and T_H2-predominant immune responses (and diseases), yet each individual may fall somewhere on the spectrum between the two poles. This may explain some of the seemingly unusual clusterings of illnesses that are seen by physicians. (Courtesy of J. Baraniuk, MD, Washington, DC.)

mucosal surfaces, and skin.¹⁶ Many humans no longer commingle with these parasites, and, instead, this highly refined and successful evolutionary system has been unleashed like a rabid Rottweiler on the dangers of modern industrialized civilization, which include devastating dust mite fecal pellets, catastrophic cat and dog dander, perilous pollen grains, and malevolent mold spores. Why these T_H2 reactions have become more prevalent in the past 3 decades is beyond the scope of this article, but is a fascinating public health challenge encircling the globe.

Returning to the focus on allergic rhinitis,⁵ several themes are developed. Sensitization leads to the development of antigen-specific T_H2 and IgE-producing B lymphocytes. Numerous factors may influence the ini-

Antigen + APC + CD8 ⁺ T _H 0 lymphocyte	
CD8⁺ Recognize "self" peptides Presented by MHC class I INF-γ, TNF-α "T_c 1" <u>Cytotoxic T cell</u> Bullous reactions, infections, neoplasia	CD8⁺ Recognize "self" peptides Presented by MHC class I INF-γ, TNF-α, IL-4, IL-5 "T_c 2" <u>Cytotoxic /</u> <u>suppressor T cell</u> Bullous reactions, eosinophilia
CD4 ⁻ CD8 ⁻ cells: recognize lipids (e.g., TB)	

Figure 3. T_c1 versus T_c2 hypothesis. The function of CD8⁺ cells is to kill resident cells expressing viral or novel tumor antigens on their class I MHC molecules. The predominant cytokine in both populations is IFN- γ . T_c2 cells, however, also express IL-4 and IL-5, which recruit eosinophils. The activity of T_c2 cells may explain the eosinophilia seen in certain tumors or in bullous skin diseases, such as poison ivy or atopic dermatitis. (Courtesy of J. Baraniuk, MD, Washington, DC.)

tial commitment of CD4 cells down pathways to T_H2 effector cells and of B cells to allergen-specific IgE-producing plasma cells (Fig. 4). Circulating IgE binds to high-affinity Fc ϵ -receptor I on mast cells and basophils. Re-exposure to allergen leads to cross-linking of these Fc receptors, and degranulation of these cells. The preformed and newly formed products are described in the next section. Stimulation of type C *itch* fibers leads to neurogenic responses. After the immediate response abates, a recruitment phase⁵ follows, with the infiltration of the tissue by eosinophils, basophils, and T_H2 cells. Their activation and mediator release during the late-phase response recapitulates much of the pathology of the immediate response. Continued allergen exposure heightens the immediate- and late-phase responses so that an exuberant chronic phase of inflammation develops. Glucocorticoids represent our current optimal palliative treatment. Their proposed mechanism of action is described in the final sections of this article. Allergy shots remain the sole treatment with the potential to desensitize and eliminate atopic responses in an allergen-specific manner.

THE CONSEQUENCES OF MAST CELL HISTAMINE RELEASE

The explosive degranulation of mast cells that follows application of allergen to the human nasal mucosa rapidly leads to itch, sneezing,

Table 2. HYPOTHETICAL MODIFICATION OF THE GELL AND COOMBS CLASSIFICATION OF IMMUNE DISEASES WITH AN EXPANSION OF TYPE IV CELLULAR IMMUNITY TO INCLUDE KNOWN T- AND B-CELL SUBSETS

Antigen Presentation		Subsets of Gell and Coombs Type IV Cellular Reactions			
Gell & Coombs Cellular Immunity		Type I-like	Type II-like	Other	
Exogenous antigen presented by Class II MHC on CD4 ⁺ cell		Delayed type hypersensitivity T _H 1 Macrophages Granulomas (e.g., TB)	Late-phase response (LPR) T _H 2 T _H 2-eosinophil infiltration (e.g., LPR of asthma)	Tolerance T _H 3?	
	Endogenous antigen presented by Class I MHC on nucleated cells to T-cell receptor on CD8 ⁺ cell	TC-1 CD8 ⁺ cell Kill antigen-presenting cell (e.g., virus infection, neoplasia, bullous skin lesions [?])	TC-2 CD8 ⁺ cell Kill antigen-presenting cell Eosinophilia (e.g., Drug reactions, neoplasia, poison ivy?)		?
Foreign lipids and polysaccharides presented by CD-1 on cutaneous (other?) Langerhans cells		?	?		CD4- CD8- (e.g., initiation of TB immune response)
Humoral Immunity		Gell and Coombs Type I Immediate Hypersensitivity	Gell and Coombs Type II Hypersensitivity	Gell and Coombs Type III Hypersensitivity	
Antigen in immune complexes or on cell surfaces. Recognized by B-cell surface IgM T-cell help, followed by heavy chain switching to IgA1, IgA2, IgG1, IgG2, IgG3, IgG4, IgD, IgE		IgE Plasma cells IgE-mast cell IgE-basophil Immediate degranulation with release of mediators of anaphylaxis. T _H 2 driven	Multiple antibody classes Recognition of self antigen with (a) Cytotoxicity (e.g., Goodpasture's syndrome) (b) Cellular activation (e.g., long-acting thyroid stimulating antibody) T helper cell driven?	Immune complex formation by IgM, IgG1, IgG3 Complement activation (e.g., anti-double stranded DNA and lupus glomerulonephritis) (e.g., serum sickness, T helper cell driven?)	
	Pseudoallergic reactions	Anaphylactoid mast cell degranulation Aspirin sensitivity	?	C3a, C5a Anaphylatoxins Mast cell degranulation Urticaria*	

*A proportion of chronic idiopathic urticaria may be owing to antithyroid IgG1 and IgG3 antibodies that cross-react with IgE-R1α leading to complement binding, activation, and release of C3a and C5a.
Courtesy of J. Baraniuk, MD, Washington, DC.

<u>Antigen</u>	+	<u>APC</u>	+	<u>Environment</u>	+	<u>Naïve T cell</u>
Extracellular		Type I versus		Type I versus		CD4
Intracellular		type II		type II		CD8
Cytoplasmic		preferring		cytokine		CD4 ⁺ CD8 ⁻
Nuclear?		Langerhans cells,		environment;		
Nucleolar?		dendritic cells,		mucosal		
Foreign		macrophages,		cutaneous		
Polysaccharide		nucleated cells,		deep tissue		
and lipids		and others		lymph node		

Figure 4. Factors affecting antigen sensitization. The nature of the antigen, its localization inside or outside of cells and on mucosal or cutaneous surfaces, and its uptake by antigen-presenting cells (APCs) help to determine the immune response that evolves toward that antigen. APCs have poorly defined preferences that lead to the predominance of type I (INF- γ) or type II (IL-4) responses. Antigen processing determines whether short antigenic peptides are presented by MHC class I (cytoplasmic or viral antigens)—which are present on all nucleated cells—or MHC class II—which are present on APCs. MHC molecules present antigen to thymus-derived naïve T cells and to antigen-specific mature T cells. It also seems that CD3⁺ cells lacking CD4 and CD8 markers may recognize foreign (e.g., tuberculoid) lipids and polysaccharides when these are presented by the primitive CD-1 antigen-presenting molecule.

nasal discharge, and mucosal swelling with increased nasal airways resistance.^{5, 52, 57} Histamine plays the preeminent role in these immediate reactions, which is clear from antihistamine studies because these drugs reduce immediate symptoms by 50% to 60%.⁵² The consequences of histamine release during the immediate phase are greater than the combined immediate effects of tryptase, prostaglandin D₂ (PGD₂), PGF₂, leukotrienes (LT) C4/D4/E4, mast cell kininogenase-mediated production of bradykinin, tumor necrosis factor- α (TNF- α), IL-4, IL-5, IL-6, transforming growth factor- β (TGF- β), and IL-13 production.⁴⁴ Histamine has synergistic effects with this melange of mediators. Leukotrienes and chymase stimulate glandular exocytosis and mucous secretion.^{27, 54} Histamine, bradykinin, leukotrienes, and platelet-activating factor (PAF) activate the endothelial cells of postcapillary venules to induce vasodilation, vascular permeability, and cellular adhesion. Contraction of postcapillary venule endothelial cells opens gaps that permit the hydrostatic intravascular pressure to force plasma into the interstitial space. A pressure of 5 mm H₂O can drive fluid from the vessels through the interstitium, across the epithelial basement membrane and between epithelial cells and their tight junctions into the nasal lumen.²¹ This is a nondamaging reversible event that is driven by hydrostatic pressure. Plasma exudation may occur without significant tissue edema. Nasal postcapillary venules also are fenestrated, which may allow the free exchange of

plasma and interstitial fluids, leading to the rapid uptake of medications and mediators that enter the lamina propria.

Histamine activates H_1 receptors on nociceptive nerve fibers to induce the sensation of itching. Histamine receptors belong to the rhodopsin receptor family, with seven transmembrane segments, an extracellular N-terminal, two extracellular loops, two intracellular loops, and a C-terminal tail.⁵² These receptors generate intracellular messages by activating guanosine triphosphate (GTP) binding protein (G-proteins). Three histamine receptors have been cloned. The H_1 receptor is the workhorse for the allergic effects of histamine. The H_2 receptor participates in stomach acid production, but also plays a role in vasodilation and possibly the cardiac effects of histamine. H_3 receptors are present on neurons, where they seem to act as *inhibitory autoreceptors* that reduce neural activity (i.e., *shut off nerves*), and in adipose tissue. H_3 inhibitory autoreceptor activity on nociceptive and parasympathetic nerves is currently subject to intense investigation in humans. Activation of these receptors may hyperpolarize these nerves and may reduce the likelihood that they can be depolarized when stimulated by nocifers such as histamine acting by way of H_1 -receptors or preganglionic neurotransmission.

H_1 receptor mRNA is up-regulated in allergic rhinitis.²⁹ H_1 receptors are present on endothelial cells, where they act to induce vascular permeability and the copious watery rhinorrhea of acute allergic rhinitis.⁴⁶ Histamine has been believed to stimulate glandular mucus production directly. Histamine, however, does not induce exocytosis in human nasal mucosal explants in vitro. Instead, it seems to activate afferent nociceptive *itch* nerves, leading to the appreciation of that sensation in the central nervous system along with recruitment of brainstem parasympathetic reflexes that are responsible for the glandular secretion component. This reflex arc supplies the rationale for using anticholinergic drugs in allergic rhinitis and in other mucus hypersecretory states.

Histamine is degraded by epithelial and endothelial histamine N-methyltransferase (HMT).⁴⁷ This action of HMT limits the duration of action of histamine in the mucosa, and explains why allergen provocation testing leads to self-limited vascular leak. Submucosal glands do not express HMT mRNA. The lack of H_1 receptors and HMT on nasal submucosal glands is consistent with the absence of histamine-induced exocytosis observed in vitro.⁴⁹

Mast cell mediator release also participates in nonatopic disorders. Anaphylactoid reactions caused by highly charged or amphipathic molecules, such as intravenous contrast dye and vancomycin (red man syndrome), are indistinguishable in their consequences from IgE-mediated mast cell degranulation. A wide range of peptides, drugs, complement factors (e.g., C3a and C5a released by immune complex formation as in serum sickness) and other IgE-independent mechanisms can trigger histamine, arachidonic acid metabolite, or cytokine release (Table 3). The difference between anaphylactic and anaphylactoid responses is the ability to demonstrate a reproducible IgE-mediated immediate mechanism.

Table 3. HISTAMINE-RELEASING FACTORS (HRF)

Direct Agonists	Augment Histamine Release	Inhibit Histamine Release
IgE-dependent HRF	IL-1 α , IL-1 β	Cromolyn
IL-1	IL-3	Nedocromil
MCP-1	IL-5	TGF- β 1
MCP-3	IL-6	TGF- β 1 antisense oligonucleotides
MIP-1 α	IL-7	Fc ϵ -R1 α antisense oligonucleotides
NAP-2	<i>c-kit</i> ligand	Isoprenaline>salmeterol>albuterol
CTAP-III		<i>Sainte</i> and <i>Val d'Orb</i> waters
C3a, C5a		Prolonged use of nonsedating antihistamines
Opioids		
Vancomycin		
Intravenous contrast dye		
High doses of substance P		
Mast cell degranulating peptide		

NOCICEPTIVE NERVE RESPONSES

In addition to directly inducing vascular permeability, histamine binds to H₁ receptors on nociceptive type C nerves. These nociceptive neurons from the first and second divisions of the trigeminal nerve are branched extensively in the epithelium and submucosal regions.⁴ In the mucosa, depolarization of the neuron may lead to the release of neurotransmitters, such as substance P (SP), calcitonin gene-related peptide (CGRP), neurokinin A (NKA), gastrin-releasing peptide (GRP), and possibly others by the axon response mechanism. These neuropeptides lead to local inflammatory responses, which are termed as *neurogenic inflammation*. The axon response has been studied extensively in rodents, and is believed to induce vascular permeability and leukocyte infiltration.⁴⁰ In normal humans and pigs, however, the axon response seems to have little if any effect on vascular leak.^{55, 56} The situation may differ in untreated severe allergic subjects who have an increase in basal plasma extravasation as a part of their allergic pathophysiology. The cause for this increase in basal vascular leak is not known, but does not seem to be related to neurogenic mechanisms.^{33, 56} This leak may be amenable to treatment with β 2-adrenergic agonists.⁴⁸ Because of this disconnection between the vascular neurogenic responses of the animal models and their apparent absence in humans, the role of the nociceptive nerve axon response in human airway mucosa has been called into question.³³ This discrepancy suggests that humans are not a suitable model for rodent neurogenic inflammation. In humans, it is likely that neurogenic inflammation is present because SP and CGRP are released within 3 minutes after allergen challenge⁴⁰ and after hypertonic saline nasal provocation.²³ An alternative hypothesis is that human airway axon responses may generate other protective effects, such as glandular

secretion and endothelial adhesion marker expression. Hypertonic saline provocation leads to pain, SP release, and glandular secretion, but does not cause changes in vascular permeability or dilation of venous sinusoids.⁶ These data indicate that in normal humans, the airway mucosal axon response induces the secretion of serous cell antibacterial enzymes, such as lysozyme, lactoferrin, and secretory IgA, plus mucin mucoglycoproteins from mucous and perhaps goblet cells.

This controversy about the roles of the axon responses in normal and inflamed nasal and bronchial mucosa likely will rage until tachykinin antagonists that block the actions of SP and other peptides are investigated in humans. Differences in neurogenic responses may be proportional to the degree of underlying mucosal inflammation because SP does have more potent effects in severe, untreated allergic rhinitis than normal subjects. Repeated SP application leads to vascular permeability, with an increase in albumin rich plasma exudation detectable in nasal lavage fluids.²² The percentages of eosinophils in nasal secretions also were significantly increased after SP treatment, increasing from approximately 18% to 42%. In vitro, treatment of human nasal mucosal explants with SP leads to significant increases in IL-1 β , IL-2, IL-3, IL-4, IL-5, IL-6, TNF- α , and IFN- γ mRNA production from allergic rhinitis nasal mucosa.⁴⁵ In tissue from nonallergic subjects, SP significantly increased only IL-6 and IL-8. This suggests that during acute inflammation, SP may have a larger effect than in nonallergic rhinitis and normal mucosa. The sites of SP-induced cytokine production may include epithelial, endothelial, and inflammatory cells in these explants.

CGRP may be the mediator of vasodilation in human nasal mucosa, and is likely to be responsible for the venous sinusoid swelling that blocks nasal airflow. It is also likely to be the mediator of the flare responses after allergen skin testing and the Triple Response of Lewis.

In the central nervous system, trigeminal nociceptive neurons enter the pons through the sensory root, and turn caudally in the trigeminal spinal tract to terminate in the pars caudalis of the nucleus of the spinal tract in the lower medulla and upper three cervical segments of the spinal cord.⁴ Pars caudalis interneurons cross the midline to enter the trigeminothalamic tract and terminate in the medial part of the ventral posterior thalamic nucleus. Painful and strong thermal stimuli are appreciated at the thalamic level. Tertiary neural relays to the lower third of the parietal cortical somesthetic areas provide for localization of nasal stimuli. Glossopharyngeal afferents innervate the posterior third of the tongue, upper pharynx, tonsils, eustachian tube, and middle ear, and also are of relevance to allergic rhinitis. These thermosensitive and nociceptive neurons terminate in the dorsal portion of the trigeminal spinal tract. Activation of these central registries is responsible for the sensations of itch and congestion that are the hallmarks of allergic rhinitis.

PARASYMPATHETIC REFLEXES

Connections between afferent trigeminal interneurons, the tractus solitarius, nucleus ambiguus, and salivatory nucleus of the seventh nerve serve to recruit parasympathetic reflexes. Seventh nerve motor fibers synapse in the sphenopalatine ganglia and pass with sympathetic fibers through the Vidian canal to enter the nasal mucosa. These postganglionic neurons contain acetylcholine, vasoactive intestinal peptide (VIP), VIP-like peptides (e.g., peptide histidine-methionine, PHM), and nitric oxide synthase (generates nitric oxide [NO]). It is possible that these are packaged in different sets of neurons. Parasympathetic reflexes are recruited rapidly after allergen challenge because VIP is released within 3 minutes after nasal allergen provocation.⁴¹

One of the most important functions of nociceptive nerves seems to be the activation of the central itch registries with recruitment of systemic reflexes such as sneezing, and organ specific parasympathetic reflexes that lead to cholinergic glandular secretion. Reflex vasodilation seems to occur, but may be of lesser functional significance. Suggestions of parasympathetic nerve-related cellular chemoattraction remain controversial.^{44, 51}

Cholinergic glandular secretion is probably the most important single tonically active influence regulating glandular exocytosis in the respiratory tract. As mentioned previously, histamine likely induces glandular secretion by activating these nociceptive-parasympathetic reflexes. This reflex provides the rationale for the use of ipratropium bromide and other anticholinergic antagonists in allergic rhinitis.¹⁰ The M3 muscarinic receptor is likely the most important of the five cloned muscarinic receptors in human nasal mucosa, based on functional and in situ hybridization studies.^{9, 59} The M2 receptor on nociceptive nerves may serve as an inhibitory autoreceptor. Eosinophil cationic proteins, such as the major basic protein, and influenza virus neuraminidase, may bind the M2 receptor and inhibit its function. This could be one example of eosinophil-mediated neural dysfunction.

LATE-PHASE AND CHRONIC ALLERGIC RHINITIS

Following the immediate phase, especially if the allergic person leaves the vicinity of the allergen, there is a diminution of symptoms. The cytokines and other mediators, however, activate endothelial and other resident cells that now act to recruit active inflammatory cells to the injured tissue. The chemokines and specific patterns of endothelial adhesion markers expressed during this recruitment phase⁵ are responsible for the accumulation of eosinophils, basophils, T_H2 cells, and other leukocytes that are found during the allergic late-phase response (Table 4). Histamine is released without a change in tryptase, suggesting release from basophils rather than a secondary degranulation of mast cells.^{26, 44, 57, 58} The role of histamine in the late-phase response is less prominent

Table 4. SUMMARY OF CYTOKINES RELEVANT TO RHINITIS

Chemokines		Inflammatory Cytokines	Fibrinogenic Cytokines	Growth Factors	Neurokines
C-X-C (α)	C-C (β)				
chromosome 4	chromosome 17				
IL-8	MCP-1	IL-1 α , β	PDGF	GM-CSF	IL-6
PF-4	MCP-3	TNF- α	IGF	G-CSF	IL-11
NAP-2	RANTES	IL-10	FGF	M-CSF	LIF
CTAP III	MIP-1 α	IL-12			CNF
(GRO-1)	IL-13				Oncostatin M
(GRO-2)	IL-15				
Lungkine					

than during the immediate phase as evidenced by the lower level of itch and sneezing. Nasal blockage develops, but it is unclear if this is because of venous sinusoid filling, nasal secretion production, or an increase in mucosal bulk caused by leukocyte invasion of the tissue.

During prolonged, recurrent, and chronic nasal allergic inflammation, histamine may be released continually. This is indicated by the benefits of prolonged antihistamine therapy. The flood of cytokines and other mediators released from infiltrating eosinophils, epithelial mast cells, and T_H2 lymphocytes in perennial rhinitis (Tables 4 and 5), however, can overwhelm the effects of histamine, leading to symptoms that are not amenable to antihistamine therapy.

HYPERRESPONSIVENESS

Hyperresponsiveness is a characteristic of mucosal surfaces during inflammation. Hyperresponsiveness indicates an increased mucosal response to nonspecific irritants such as histamine; methacholine; bradykinin; hypertonic saline; cold, dry air; and other provocative agents.^{12, 60} Allergic rhinitis subjects have increased glandular secretion when stimulated with endothelin-1, bradykinin, and histamine. Stimulation of nociceptive nerves with recruitment of parasympathetic reflexes is the postulated mechanism. Glandular responses to methacholine also are

Table 5. NONLYMPHOID SOURCES OF CYTOKINES

Macrophage	Epithelium	Eosinophils	Mast Cells
IL-12	GM-CSF	IL-5	IL-3
IFN- α	IL-6	GM-CSF	IL-4
TNF- α	IL-8	TNF- α	IL-5
Eotaxin	Eotaxin	Eotaxin	TNF- α
			TGF- β
			IL-13
			IL-6

increased.¹⁹ VIP-immunoreactive nerve fibers also may be increased in density, which has been suggested for chronic bronchitis and cholinergic nonallergic rhinitis.^{37, 38} VIP has been proposed as an additional glandular secretagogue that participates in parasympathetic reflexes. In contrast to glandular hypersecretion, histamine-induced vascular permeability and exudative hyperresponsiveness does not seem to involve nociceptive axon responses or other neural effects.⁵⁶

The molecular mechanisms underlying the increase in nociceptive nerve sensitivity to these nocifers (agents that stimulate nociceptive nerves), the increases in the parasympathetic reflex components, and changes in mucosal mucus production and secretory processes still remain to be defined. When inflammatory mediators bind to their specific neurokinin-1 (NK-1), histamine H₁, muscarinic M3, bradykinin B2, and other 7-transmembrane receptors, conformation changes induced in the receptor lead to activation of the intracellular GTP-binding $\alpha\beta\gamma$ -trimeric G-proteins that associate with the third intracellular loop of these receptors. This, in turn, leads to a cascade of signal transduction effects that can activate transcription factors, such as the immediate early genes *c-fos* and *c-jun* that form the activating protein-1 (AP-1) complex, and the release of active nuclear factor- κ B (NF- κ B) from its inhibitor (I κ B). Other transduction pathways also play roles in cellular activation in atopy. These transcript factors bind to promoters of a wide range of genes in the nucleus, leading to the production of additional proinflammatory proteins, receptors, and mediators (Fig. 5). Cytokines have other transduction pathways that lead to the further up-regulation of mRNA production. In general, mRNA transcription requires continued proinflammatory mediator release and receptor binding with transcription factor activation to be maintained.

Nociceptive nerve responses and neurogenic inflammation may be up-regulated by neurotrophic cytokines such as nerve growth factor (NGF) and IL-11 (Table 4). IL-11 may participate in the pathogenesis of viral rhinitis and asthma.²⁰ Nasal instillation of IL-11 in mice leads to cholinergic bronchial reactivity with minimal peribronchial infiltrates 24 hours later. Children with common colds who have elevated IL-11 concentrations in their nasal secretions are more likely to develop asthma. The asthmatic subset also had significantly increased IL-11 lavage levels compared with those who did not develop wheezing. The role of IL-11 and similar cytokines requires further investigation in allergic rhinitis.

In contrast to this hyperresponsiveness, hyporesponsiveness also can occur. For example, in chronic sinusitis, patients have high baseline secretion of glandular products, but have no reserve to exocytose additional materials when challenged with the glandular secretagogue methacholine.³¹ This finding suggests that the glands were acting at their maximal rate of exocytosis because of high mucosal secretagogue levels, or that they had developed tachyphylaxis or unresponsiveness to further muscarinic challenge.

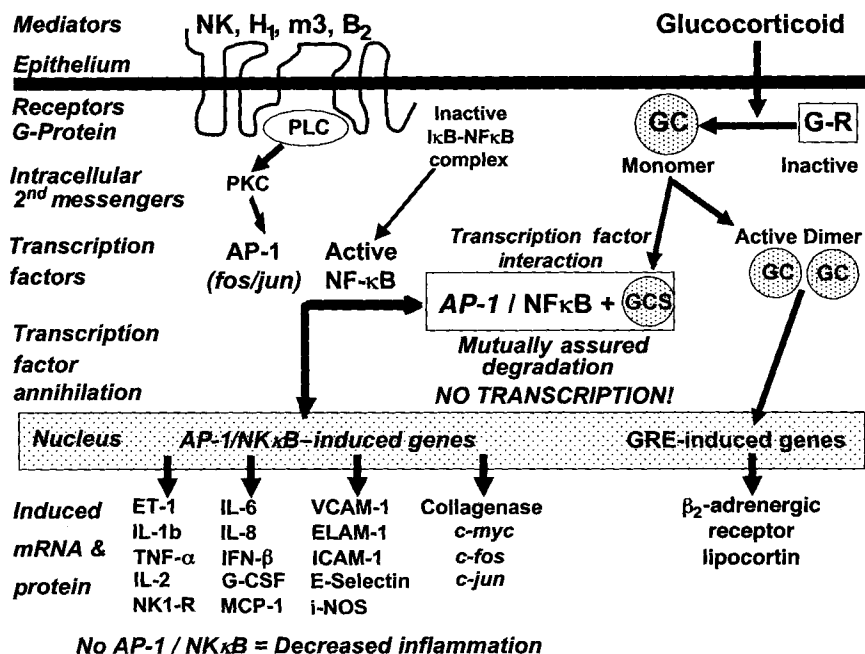


Figure 5. Hypothesis: *c-fos* and *c-jun* heterodimers form activating protein-1 (AP-1) that interacts with glucocorticoids. Activation of neurokinin (NK), H₁, muscarinic m3, bradykinin B₂, and other 7-transmembrane receptors leads to the activation of *c-fos* and *c-jun* and to the formation of AP-1 (left). AP-1 participates in the induction of various proinflammatory proteins, receptors, and mediators. Glucocorticoids bind to cytoplasmic receptors, which dimerize and translocate to the nucleus to induce genes, such as the β₂-adrenergic receptor (right). AP-1 and activated glucocorticoid receptors can bind to each other, leading to their mutual proteolytic degradation and the loss of their nuclear transcription factor effects. (Courtesy of J. Baraniuk, MD, Washington, DC.)

THERAPEUTIC MECHANISMS

Intranasal glucocorticoids remain the premier topical anti-inflammatory drugs for allergic rhinitis. They are effective at reducing basal vascular leak in allergic rhinitis and allergen-induced nasal hyper-responsiveness.^{1, 12} Steroids reduce the densities of mucosal mast cells, dendrite cells, lymphocytes, and eosinophils in the epithelium, which leads to a decrease in proinflammatory mediator release. Glucocorticoids also modulate *c-fos*, *c-jun*, and NF-κB activities in inflammatory and resident cells (Fig. 5). The steroids bind to cytoplasmic glucocorticoid receptors, which dissociate from heat shock proteins, dimerize, and translocate to the nucleus.³ There, this complex acts on glucocorticoid response elements in promoters of genes, such as the β₂-adrenergic receptor, and increase their expression. The most critical anti-inflammatory action of steroids is mediated by the interactions between the

activated glucocorticoid receptor monomers and AP-1, NF- κ B, and other proinflammatory gene-activating factors. These interactions lead to mutual proteolytic degradation, and the loss of all transcriptional activity for each factor. As an example, nasal steroids reduce the expression of epithelial *c-fos*-immunoreactive material in human nasal polyps *in vivo*.¹¹

The benefits of antihistamines have focused on treatment of itch and vascular permeability. These benefits are shared by sedating and nonsedating second-generation antihistamines. The older drugs are less specific for the H₁ receptor and also block other receptors. The anticholinergic effects of brompheniramine and chlorpheniramine have been demonstrated. They are about 19 times less potent than atropine in a model of methacholine-induced glandular secretion from human nasal mucosal explants *in vitro*.²⁴ These older antihistaminics may offer some advantages for patients with allergic rhinitis and mucous hypersecretion who are more resistant to the sedating side effects. The sedation may be related to the antihistaminic and anticholinergic properties of these drugs in the central nervous system. Several other treatments also may assist in reducing the potency of histamine's effects. Allergy shots reduce histamine, bradykinin, and TAME-esterase concentrations in nasal lavage fluids collected during the immediate and early phases after nasal allergen challenge.²⁸

The search for drugs to inhibit mast cell degranulation began with cromolyn, but continues now with mixed success. TGF- β 1¹⁴ or, contrarily, antisense oligonucleotides to TGF- β 1,³⁵ may inhibit histamine release. Sufficiently high doses of β 2-adrenergic agonists also may be successful,⁴⁸ although in isolated human lung mast cells the rank potency for inhibition of mediator release was isoproterenol greater than salmeterol, salmeterol greater than salbutamol.¹⁶ Healing therapeutic waters,³² herbal remedies, and prolonged use of nonsedating antihistamines³⁰ have been reported to reduce the release of histamine and other mediators from rat and human mast cells in a number of *in vivo* and *in vitro* systems. These reports must be viewed, however, with deep skepticism until their claims are examined by double-blind placebo-controlled trials in allergic rhinitis. It is anticipated that the molecular biology explosion that is engulfing medical research will lead to exciting and revolutionary new drugs and new concepts of antiallergic and anti-inflammatory therapy. For the sufferer of allergic rhinitis, however, these "wonder drugs" may not be marketed for 5 to 15 years, based on the current rate of development and regulatory review separating the bench from the bedside.

References

1. Altman LC, Ayars GH, Baker C, et al: Cytokines and eosinophil derived cationic proteins up-regulate intercellular adhesion molecule 1 on human nasal epithelial cells. *J Allergy Clin Immunol* 92:527-536, 1993
2. Andersson M, Greiff L, Svensson C, et al: Allergic and nonallergic rhinitis. In Busse WW, Holgate ST (eds): *Asthma and Rhinitis*. Boston, Blackwell Scientific Publications, 1995, pp 145-155

3. Baraniuk JN (ed): Glucocorticoids: Bench to bedside. *J Allergy Clin Immunol* 97:141–182, 1996
4. Baraniuk JN: Neuropeptide pharmacology. In Townley RG, Agarwal DK (eds): *Immunopharmacology of the Respiratory Tract: Clinical Allergy and Immunology*. 1996, pp 575–603
5. Baraniuk JN: Pathogenesis of allergic rhinitis. *J Allergy Clin Immunol* 99:S763–S772, 1997
6. Baraniuk JN, Ali M, Yuta A, et al: Hypertonic saline nasal provocation stimulates nociceptive nerves, substance P release, and glandular mucus exocytosis in normal humans. *Am J Respir Crit Care Med* 160:655–662, 1999
7. Baraniuk JN, Clauw JD, Gaumond E: Rhinitis symptoms in chronic fatigue syndrome. *Ann Allergy Asthma Immunol* 81:359–365, 1998
8. Baraniuk JN, Clauw D, Yuta A, et al: Nasal secretion analysis in allergic rhinitis, cystic fibrosis, and nonallergic fibromyalgia: Chronic fatigue syndrome subjects. *Am J Rhinol* 12:435–440, 1998
9. Baraniuk JN, Kaliner MA, Barnes PJ: Localization of m3 muscarinic receptor mRNA in human nasal mucosa. *Am J Rhinol* 6:145–148, 1992
10. Baraniuk JN, Silver PB, Kaliner MA, et al: Effects of ipratropium bromide on bradykinin nasal provocation in humans. *Clin Exp Allergy* 14:724–729, 1994
11. Baraniuk JN, Wong G, Ali M, et al: Glucocorticoids decrease *c-fos* expression in human nasal polyps in vivo. *Thorax* 53:577–582, 1998
12. Baroody FM, Cruz AA, Lichtenstein LM, et al: Intranasal beclomethasone inhibits antigen induced nasal hyperresponsiveness to histamine. *J Allergy Clin Immunol* 90:373–376, 1992
13. Biedlingmaier JF, Trifillis A: Comparison of CT scan and electron microscopic findings on endoscopically harvested middle turbinates. *Otolaryngol Head Neck Surg* 118:165–173, 1998
14. Bissonette EY, Encisco JA, Befus AD: TGF-beta-1 inhibits the release of histamine and tumor necrosis factor-alpha from mast cells through and autocrine pathway. *Am J Respir Cell Mol Biol* 16:275–283, 1997
15. Bonini S, Bonini O, Lambiasi A, et al: Vernal keratoconjunctivitis: A model of 5q cytokine gene cluster disease. *Int Arch Allergy Immunol* 107:95–98, 1995
16. Chong LK, Cooper E, Vardey CJ, et al: Salmeterol inhibition of mediator release from human lung mast cells by beta-adrenoceptor-dependent and independent mechanisms. *Br J Pharmacol* 123:1009–1015, 1998
17. Coombs RRA, Gell PGH: The classification of allergic reactions underlying disease. In Gell PGH, Coombs RRA (eds): *Clinical Aspects of Immunology*. Oxford, Blackwell Scientific Publications, 1963, pp 317–337
18. Druce HM: Allergic and nonallergic rhinitis. In Middleton E, Jr, Reed CE, Ellis E, et al (eds): *Allergy Principles and Practice* ed. 4. St. Louis, Mosby, 1993, pp 1433–1453
19. Druce HM, Wright RH, Kossoff D, et al: Cholinergic nasal hyperreactivity in atopic subjects. *J Allergy Clin Immunol* 76:445–452, 1985
20. Einarsson O, Geba GP, Zhou Z, et al: Interleukin-11 in respiratory inflammation. *Ann NY Acad Sci* 762:31–40, 1995
21. Erjefält I, Persson CGA: Allergen, bradykinin, and capsaicin increase outward but not inward macromolecular permeability of guinea-pig tracheobronchial mucus. *Clin Exp Allergy* 21:217–224, 1991
22. Fajac I, Braunstein G, Ickovic MR, et al: Selective recruitment of eosinophils by substance P after repeated allergen exposure in allergic rhinitis. *Allergy* 50:970–975, 1995
23. Fang S-Y, Ali M, Yuta A, et al: Hypertonic saline nasal provocation induces substance P release: Airway neurogenic inflammation redefined. *Am J Respir Crit Care Med* 157(abstract):487, 1998
24. Fang S-Y, Druce HM, Baraniuk JN: Anticholinergic properties of brompheniramine, chlorpheniramine and atropine in human nasal mucosa in vitro. *Am J Rhinol* 12:131–133, 1998
25. Frazer KA, Ueda Y, Zhu Y, et al: Computational and biological analysis of 680 kb of

- DNA sequence from the human 5q31 cytokine gene cluster region. *Genome Research* 7:495-512, 1997
26. Gosset P, Malaquin F, Delnest Y, et al: Interleukin 6 and interleukin 1 production is associated with antigen induced late nasal response. *J Allergy Clin Immunol* 92:878-890, 1993
 27. Holgate ST, Bradding BM, Sampson AP: Leukotriene antagonists and synthesis inhibitors: New directions in asthma therapy. *J Allergy Clin Immunol* 98:1-13, 1996
 28. Iliopoulos O, Proud D, Adkinson F, Jr, et al: 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* 87:855-866, 1991
 29. Iriyoshi N, Takeuchi K, Yuta A, et al: Increased pathology of allergic rhinitis: Expression of histamine H1 receptor mRNA in allergic rhinitis. *Clin Exp Allergy* 26:379-385, 1996
 30. Jacobi HH, Skov PS, Poulsen LK, et al: Histamine and tryptase in nasal lavage fluid after allergen challenge: Effect of 1 week of pretreatment with intranasal azelastine or systemic cetirizine. *J Allergy Clin Immunol* 103:768-772, 1999
 31. Jeney EV, Raphael GD, Meredith SD, et al: Abnormal cholinergic parasympathetic responsiveness in the nasal mucosa of patients with recurrent sinusitis. *J Allergy Clin Immunol* 86:10-18, 1990
 32. Joly F, Charveron M, Aries MF, et al: Effect of Avene spring water on the activation of rat mast cell by substance P or antigen. *Skin Pharmacol Appl Skin Physiol* 11:111-116, 1998
 33. Joos GF, Germonpre PR, Pauwels RA: Neurogenic inflammation in human airways: It is important? *Thorax* 50:217-219, 1995
 34. Kaliner MA: Allergic rhinitis. In Mygind N, Naclerio RM (eds): *Allergic and Non-Allergic Rhinitis—Clinical Aspects*. Philadelphia, WB Saunders, 1993, pp 152-158
 35. Kim HM, Lee YM: Role of TGF-beta-1 on the IgE-dependent anaphylaxis reaction. *J Immunology* 162:4960-4965, 1999
 36. Kruskal J, Xiong M, Ferrell R, et al: Linkage and association of adrenergic and dopamine receptor genes in the distal portion of the long arm of chromosome 5 with systemic blood pressure variation. *Hum Mol Genet* 7:1379-1383, 1998
 37. Kurian SS, Blank MA, Sheppard MN: Vasoactive intestinal polypeptide (VIP) in vasomotor rhinitis. *Clin Biochem* 11:425-426, 1983
 38. Lucchini RE, Facchini F, Turato G, et al: Increased VIP-positive nerve fibers in the mucous glands of subjects with chronic bronchitis. *Am J Respir Crit Care Med* 156:1963-1968, 1997
 39. Mareni C, Sessarego M, Montera M, et al: Expression and genomic configuration of GM-CSF, IL-3, M-CSF receptor (C-FMS), early growth response gene-1 (EGR-1) and M-CSF genes in primary myelodysplastic syndromes. *Leuk Lymphoma* 15:135-141, 1994
 40. McDonald DM: Neurogenic inflammation in the respiratory tract: Actions of sensory nerve mediators on blood vessels and epithelium of the airway mucosa. *Am Rev Respir Dis* 136(suppl):65-72, 1987
 41. Mossiman BL, White MV, Hohman RJ, et al: Substance P, calcitonin-gene related peptide, and vasoactive intestinal peptide increase in nasal secretions after allergen challenge in atopic patients. *J Allergy Clin Immunol* 92:95-104, 1993
 42. Mullol J, Baraniuk JN, Logun C, et al: M1 and M3 muscarinic antagonists inhibit human nasal glandular secretion in vitro. *J Appl Physiol* 73:2069-2073, 1992
 43. Mygind N, Dahl R, Pedersen S, et al: *Essential Allergy*, ed 2. Oxford, Blackwell Science, 1996, pp 206-208
 44. Naclerio RM, Baroody FM, Kagey-Sobotka A, et al: Basophils and eosinophils in allergic rhinitis. *J Allergy Clin Immunol* 94:1303-1309, 1994
 45. Okamoto Y, Shirotori K, Kudo K, et al: Cytokine expression after the topical administration of substance P to human nasal mucosa: The role of substance P in nasal allergy. *J Immunol* 151:4391-4398, 1993
 46. Okayama M, Baraniuk JN, Hausfeld JN, et al: Characterization and autoradiographic localization of histamine H1 receptors in human nasal turbinates. *J Allergy Clin Immunol* 89:1144-1150, 1992

47. Okayama M, Yamauchi K, Sekizawa K, et al: Localization of histamine N-methyltransferase messenger RNA in human nasal mucosa. *J Allergy Clin Immunol* 95:96-102, 1995
48. Proud D, Reynolds CJ, Lichtenstein LM, et al: Intranasal salmeterol inhibits allergen-induced vascular permeability but not mast cell activation or cellular infiltration. *Clin Exp Allergy* 28:868-875, 1998
49. Raphael GD, Meredith SD, Baraniuk JN, et al: The pathophysiology of rhinitis II: Assessment of the sources of protein in histamine-induced nasal secretions. *Am Rev Respir Dis* 139:791-800, 1989
50. Riccio MM, Proud D: Evidence that enhanced nasal reactivity to bradykinin in patients with symptomatic allergy is mediated by neural reflexes. *J Allergy Clin Immunol* 97:1252-1263, 1996
51. Sanico AM, Atsuta S, Togias A: Leukocyte influx after capsaicin nasal challenge is a dose dependent phenomenon. *J Allergy Clin Immunol* 97:430, 1996
52. Simons E, Simons K (eds): *Histamine and H1-Antagonists in Allergic Disease*. New York, Marcel Dekker, 1996, 1-424
53. Smirnov DV, Smirnova MG, Korobko VG, et al: Tandem arrangement of human genes for interleukin-4 and interleukin-13: Resemblance in their organization. *Gene* 155:277-281, 1995
54. Sommerhof CP, Caughey GH, Finkbeiner WE, et al: Mast cell chymase: A potent secretagogue for airway gland serous cells. *J Immunol* 142:2450-2456, 1989
55. Stjarne P, Lacroix JS, Ånggård A, et al: Compartment analysis of vascular effects of neuropeptides and capsaicin in the pig nasal mucosa. *Acta Physiol Scand* 141:335-342, 1991
56. Svensson C, Andersson M, Greiff L, et al: Exudative hyperresponsiveness of the airway microcirculation in seasonal allergic rhinitis. *Clin Exp Allergy* 25:942-950, 1995
57. Terada N, Kono A, Togawa K: Biochemical properties of eosinophils and their preferential accumulation mechanism in nasal allergy. *J Allergy Clin Immunol* 94:629-642, 1994
58. Togias A: Non-allergic rhinitis. *In* Mygind N, Naclerio RM (eds): *Allergic and Non-Allergic Rhinitis: Clinical Aspects*. Philadelphia, WB Saunders, 1993, pp 159-166
59. Togias A, Naclerio RM, Proud D, et al: Studies on allergic and nonallergic nasal inflammation. *J Allergy Clin Immunol* 81:782-790, 1988
60. White MV: Nasal cholinergic hyperresponsiveness in atopic subjects studied out of season. *J Allergy Clin Immunol* 92:278-287, 1993

Address reprint requests to

James N. Baraniuk, MD
Division of Rheumatology, Immunology, and Allergy
Georgetown University
LL Gorman Building
3800 Reservoir Road
Washington, DC, 20007-2197

e-mail: baraniuj@gunet.georgetown.edu