INTRODUCTION

From the perspective of the environment, the nose serves as the portal of entry to the respiratory tract, filtering and conditioning inspired air, as well as signaling the quality of the surrounding atmosphere. In this exposed position, the nose is vulnerable to the effects of physical or chemical agents, and may manifest acute, subacute, or chronic pathophysiologic changes.

Individuals who experience acute and reversible nasal symptoms (obstruction and/or hypersecretion) triggered by ambient physical or chemical exposures, and who do so without evidence of a typical allergic (immunoglobulin [Ig]E-mediated) mechanism, can be considered to have “environmental nonallergic rhinitis” (“environmental NAR”).
The state of exaggerated nasal reflexes underlying this condition is referred to as nonspecific nasal hyperreactivity. Such hyperreactivity is also reported by a significant subset of allergic rhinitis (AR) patients, rendering the condition more a phenotypic trait than a specific response mechanism.

This article deals with the topic of environmental NAR. The objective of this article is to review the epidemiology, clinical manifestations, and unique mechanistic features of environmental NAR, and in particular to catalog the range of environmental exposures that may prove problematic to individuals with idiopathic NAR.

BACKGROUND: ANATOMY, PHYSIOLOGY, AND REGIONAL DEPOSITION OF AIR POLLUTANTS

The functional anatomy of the nose includes the extensive mucosal area of the turbinates, providing for warming and humidification of inspired air, as well as for removal of particulate and gaseous phase air pollutants. In the process, physical and chemical stimuli can elicit specific nasal sensations, including olfaction, warming or cooling, irritation and, less typically, nasal pruritus. Conveying these sensations, the nasal cavity is innervated by 2 main structures: the olfactory nerve (cranial nerve I, providing for the sense of smell), and the trigeminal nerve (cranial nerve V, providing for the sense of temperature and irritation; Fig. 1). Just as our appreciation of foods involves a combination of the senses of taste and smell, our appreciation of many inhaled compounds involves both olfaction and trigeminal stimulation. The latter carries sensations ranging from “freshness” or “cooling” (eg, in response to menthol) to burning or stinging (as elicited by ammonia or chlorine).

Of relevance, our understanding of the peripheral neurobiology of trigeminal chemoreception has benefitted from significant molecular biologic developments over the last 2 decades. We have learned that the small diameter nociceptive neurons (C- and Aδ-fibers) constituting the terminal branches of the trigeminal nerve are invested with wide variety of nociceptive ion channels with both thermal and chemical responsiveness. The C-fiber population also elaborates vasoactive neuropeptides, which in turn can be released locally as part of nociceptive reflexes. More recently,

![Fig. 1. Innervation of the nasal cavity. Cr. N. I, olfactory nerve; Cr. N. V, trigeminal nerve. (From Shusterman D. The upper airway, including olfaction, as mediator of symptoms. Environ Health Perspect 2002;110(Suppl 4):649–53.)](image-url)
solitary chemosensory cells, with the capacity to sense both airborne irritants and bitter tastants, have also been documented in the human nasal mucosa. Central and peripheral reflexes arising from nasal mucosal nerve stimulation include sneezing, rhinorrhea, nasal obstruction (“congestion”), cough, bronchospasm, and laryngospasm. Although the vast majority of these reflexes are thought to be neurogenic in nature, the mechanism(s) underlying reflex nasal obstruction are less clear cut, as noted elsewhere in this paper.

The term “sensory irritation” is used by environmental scientists to describe trigeminally mediated mucous membrane (eye, nose, and throat) irritation, a symptom constellation common in so-called problem buildings. Although rhinorrhea and nasal congestion are typical presenting complaints in environmental NAR, nasal hyperesthesia may, in fact, constitute the primary symptom in some patients, along with the related phenomenon of odor intolerance. Although odor intolerance is beyond the scope of this review, irritation and nasal hyperesthesia are relevant to an understanding of environmental NAR. Neurobiological terms that have been invoked to explain nasal hyperesthesia and/or hyperreactivity after allergic or irritant stimulation include “neuromodulation,” “phenotypic switching,” and “central sensitization.”

Both physical and chemical stimuli can trigger nasal reflexes, including nasal secretion and obstruction. Classic examples include rhinorrhea occurring in response to consumption of spicy foods (“gustatory rhinitis”) and cold air–induced rhinorrhea (“skier’s nose”), both of which can be blocked symptomatically by the topical application of a cholinergic antagonist. This clinical response, as well as the results of numerous nasal provocation experiments, have implicated a central parasympathetic reflex in most reflex rhinorrhea. Nonallergically triggered nasal obstruction, on the other hand, ultimately reflecting vasodilation and/or plasma extravasation, has less clear reflex mechanisms.

In addition to acute and reversible symptom triggering (as in neurogenic inflammation), the rubric of environmental NAR can also encompass irritant-induced pathologic changes. For example, nasal mucosal swelling, whether from allergy, infection, or nonallergic reflexes, can potentially interfere with Eustachian tube and sinus ostial patency, thereby producing pressure disequilibrium in the middle ear and paranasal sinuses, and associated signs and symptoms otitis media or sinusitis. Furthermore, exposures to photochemical oxidant air pollutants can produce actual histologic changes in the nasal mucosa, as reviewed elsewhere in this paper. In terms of exposures, irritant air pollutants include, in addition to “criteria air pollutants” (ozone, nitrogen oxides, sulfur dioxide, and particulate matter), a variety of industrial chemicals, combustion products (smokes and fumes), cleaning chemicals, and volatiles evolved by building materials and/or microbial growth (Tables 1 and 2).

When considering the impact of air pollutants on the upper airway, whether from vapors, gases, smokes, or fumes, regional dosimetry is an important consideration. With reference to particulate matter, the upper airway is disproportionately affected by large particles (ie, those >5–10 μm in diameter; Fig. 2). The regional deposition of gases and vapors, on the other hand, is dominated by the property of water solubility, with highly water-soluble compounds readily dissolving in mucus and thence activating upper airway mucosal irritant receptors (Fig. 3). Clearance of highly water-soluble gases and vapors in the upper airway (“scrubbing”) can also be significant. For chlorine gas, for example, more than 90% of an inhaled bolus at concentrations up to 3 ppm is cleared above the larynx (ie, before entering the large conductive airways of the lower respiratory tract).
### Table 1
Environmental irritants

<table>
<thead>
<tr>
<th>Source or Class</th>
<th>Specific Pollutant</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combustion Products</td>
<td>Second-hand tobacco smoke</td>
<td>Complex mixture of vapors, gases, and particulates</td>
</tr>
<tr>
<td></td>
<td>NOx</td>
<td>Unvented stoves and heaters</td>
</tr>
<tr>
<td></td>
<td>SOx</td>
<td>Vehicular exhaust</td>
</tr>
<tr>
<td></td>
<td>Ozone + PAN</td>
<td>Photochemical reaction products of VOCs + NOx from vehicular exhaust</td>
</tr>
<tr>
<td></td>
<td>Particulate matter</td>
<td>Fireplaces and wood-burning stoves; power plants; diesel engines</td>
</tr>
<tr>
<td>Cleaning products</td>
<td>Hypochlorite, ammonia</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Chloramines, chlorine gas</td>
<td>Reaction products of inappropriate mixing</td>
</tr>
<tr>
<td>VOCs</td>
<td>Formaldehyde, a glycol ethers, various others</td>
<td>Off-gassing construction materials and furnishings</td>
</tr>
<tr>
<td></td>
<td>Various</td>
<td>Stationary and art materials; polishes and waxes</td>
</tr>
<tr>
<td></td>
<td>MVOCs</td>
<td>Microbial VOCs (byproducts of mold growth)</td>
</tr>
</tbody>
</table>

**Abbreviations:** MVOCs, volatile organic compounds of microbial origin; NOx, nitrogen oxides; PAN, peroxyacetyl nitrite; SOx, sulfur oxides; VOCs, volatile organic compounds.

* The formaldehyde content of pressed-board products is regulated by the US Consumer Products Safety Commission.


### Table 2
Selected occupational irritants

<table>
<thead>
<tr>
<th>Occupation</th>
<th>Irritant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agricultural workers</td>
<td>Ammonia, nitrogen dioxide, hydrogen sulfide</td>
</tr>
<tr>
<td>Custodians</td>
<td>Ammonia, bleach (hypochlorite), chloramines</td>
</tr>
<tr>
<td>Firefighters</td>
<td>Smoke, hazardous materials releases</td>
</tr>
<tr>
<td>Food service workers</td>
<td>Cooking vapors, cigarette smoke</td>
</tr>
<tr>
<td>Health professionals</td>
<td>Glutaraldehyde, formaldehyde</td>
</tr>
<tr>
<td>Laboratory workers</td>
<td>Solvent vapors, inorganic acid vapors/mists</td>
</tr>
<tr>
<td>Military personnel</td>
<td>Zinc chloride smoke</td>
</tr>
<tr>
<td>Power plant and oil refinery workers</td>
<td>Sulfur dioxide</td>
</tr>
<tr>
<td>Printers, painters</td>
<td>Solvent vapors</td>
</tr>
<tr>
<td>Pulp mill workers</td>
<td>Chlorine, chlorine dioxide, hydrogen sulfide</td>
</tr>
<tr>
<td>Railroad personnel, miners, truck drivers</td>
<td>Diesel exhaust</td>
</tr>
<tr>
<td>Refrigeration workers (commercial)</td>
<td>Ammonia</td>
</tr>
<tr>
<td>Roofers, pavers</td>
<td>Asphalt vapors, PAHs a</td>
</tr>
<tr>
<td>Swimming pool service workers</td>
<td>Chlorine, hydrogen chloride, nitrogen trichloride</td>
</tr>
<tr>
<td>Waste water treatment workers</td>
<td>Chlorine, hydrogen sulfide</td>
</tr>
<tr>
<td>Welders</td>
<td>Metallic oxide fumes, nitrogen oxides, ozone</td>
</tr>
<tr>
<td>Woodworkers</td>
<td>Wood dust</td>
</tr>
</tbody>
</table>

* Polycyclic aromatic hydrocarbons (also skin and lung carcinogen).

EPIDEMIOLOGY OF NONALLERGIC RHINITIS

Estimates of the prevalence of NAR in industrialized countries vary considerably. A population-based study of adults conducted in Sweden, for example, found the self-reported prevalence of NAR to be 19%, approaching the prevalence of 24% for allergic rhinoconjunctivitis. Analysis of data across age groups in the United States,

Fig. 2. Regional deposition of particles within the respiratory tract, by particle diameter. (Data from Zhao YA, Shusterman D. Work-related upper respiratory tract conditions. Clin Chest Med 2012;33:637–47.)

Fig. 3. Water solubility and site of initial impact of airborne irritants. (From Zhao YA, Shusterman D. Occupational rhinitis and other work-related upper respiratory tract conditions. Clin Chest Med 2012;33:637–47.)
on the other hand, points to a population prevalence of AR of 20%, NAR of 7%, and “mixed” rhinitis (AR with prominent nonallergenic triggers) of 9%, with a total of 16% of the population having either NAR or “mixed” rhinitis.29 Looked at from a different perspective, AR patients (the largest subgroup of rhinitis patients) are between 40% to 67% likely to report both allergic and nonallergenic triggers, making the identification of a single underlying mechanism for nonspecific nasal hyperreactivity an elusive task.6,7 Demographic risk factors for the development of NAR include female gender and advancing age.30

SYMPTOM TRIGGERS AND OTHER ENVIRONMENTAL INCITANTS

Symptom triggering (and other nonallergenic upper airway health effects) have been addressed in NAR using 3 main study designs:

1. Symptom surveys of patients;
2. Observational studies correlating symptoms or biomarkers with environmental measurements; and
3. Controlled human exposure studies.

These 3 study types are considered individually in the following subsections.

Symptom Surveys of Patients

Shusterman and Murphy7 ascertained the prevalence of nonallergenic symptom triggers among 60 adults, including 31 with seasonal AR (SAR) and 29 nonrhinitis (NR), nonatopic controls. All subjects were nonsmokers without a history of occupational exposure to irritants. Overall, the number of self-reported nonallergenic triggers was bimodal, with peaks at 1 and 5 (of a possible 8). Forty-two percent of SAR subjects reported more than 3 nonallergenic triggers, compared with only 3% of NR controls (P < .01). The relative order of trigger reporting for SAR and NR subjects was identical (spicy foods > changes in temperature and humidity > environmental tobacco smoke = exercise > household cleaning products = perfumes and colognes > alcohol consumption > bright lights), with all triggers except spicy food and bright lights being significantly more prevalent among SAR subjects than controls. Subjects over 35 years of age were more likely to report one or more nonallergenic triggers, particularly second-hand tobacco smoke (P < .05).7

Segboer and colleagues6 administered a symptom (trigger) questionnaire to 585 consecutively referred AR and 408 NAR patients. The 2 groups showed no difference in the prevalence of nonspecific symptom triggering, with greater than 60% of both groups reporting a response to at least one nonallergenic trigger. The relative importance of various triggers was also indistinguishable between the 2 subgroups (ie, temperature changes > smoke or smells > exercise > emotional stress > humidity). In a substudy of 18 AR, 21 NAR, and 17 healthy control patients, both rhinitis subgroups reported significant increases in subjective rhinorrhea, burning, and nasal secretion after cold, dry air (CDA) exposure, with a significant increase in self-reported congestion in the AR group only. However, neither rhinitis group showed significant changes in nasal peak inspiratory flow post-CDA challenge.

Bernstein and colleagues31 compared the characteristics 404 patients with physician-diagnosed chronic AR, 123 NAR, and 129 mixed rhinitis before and after stratifying patients using an “irritant index questionnaire” in conjunction with a skin prick test. Principle component analysis was performed to determine discriminating cut points between allergic and NAR. They found that a significant number of rhinitis
patients were reclassified based on having a high or low irritant index score, resulting in 4 groups: AR without and with a high irritant index score (ie, AR and mixed rhinitis) and NAR with and without a high irritant index score. In contrast with correlations for the consensus diagnoses, the reclassified AR and NAR patients with high irritant index scores had more severe and more frequent rhinitis symptoms and a greater likelihood of physician-diagnosed asthma.

**Observational Studies**

Numerous observational (epidemiologic) studies have addressed the nasal effects of physical and/or chemical aspects of ambient or indoor air quality. In some studies, individual factors (age, gender, or rhinitis status) were examined as potential markers of differential susceptibility. Although many of these studies have focused on single aspects of the inspired atmosphere (eg, meteorology, ozone [O₃] levels, presence of wet and/or moldy indoor conditions), potential confounding is always a concern in epidemiologic investigations. We have presented herein a selective sample of these studies (Table 3).

**Ambient air quality**

Hoshino and colleagues performed a retrospective chart review of outpatients in a general medicine clinic over a 1-year period, examining unscheduled visits for NAR. A time-series analysis was conducted comparing visit incidence with air temperature, humidity ("vapor pressure"), and various air pollution indices. Significantly more visits occurred during periods with exaggerated diurnal temperature variation, during cold, dry weather, high winds, and with high concentrations of photochemical oxidants.

Braat and colleagues performed a time-series analysis of nasal symptoms recorded on a daily basis over a 7-month period among 16 NAR patients and 7 normal controls, correlating symptoms with daily measurements of temperature, humidity, and air pollutant levels. After correcting for autocorrelation and introducing optimal lag times, NAR patients’ symptoms were predicted by minimum daytime temperature, average daytime relative humidity (%), O₃ levels, and particulate matter of 10 microns in diameter or smaller.

In a series of related studies, Calderon-Garciduenas and colleagues have examined the upper airway impact of air pollutants in Mexico City (including O₃, particulate matter, and aldehydes). One such study compared urban residents with residents of an unpolluted locale, revealing squamous metaplasia, loss of normal cilia, vascular congestion, and glandular atrophy on nasal biopsy of the urban residents. Another study examined visitors to the city who came from a more rural areas; such short-term visitors developed epithelial desquamation and neutrophilic inflammation that took more than 2 weeks to resolve after returning to their home towns. Additional studies identified ultrastructural abnormalities of both cellular maturation and ciliary morphology, as well as evidence p53 tumor suppressor protein activation among Mexico City residents versus controls.

Kopp and colleagues studied the effects of varying atmospheric O₃ levels on the upper airway by examining serial nasal lavage specimens collected over a 7-month period from nonatopic school children in Germany. The investigators found an initial increase in nasal leukocytes and eosinophilic cationic protein with the initial seasonal increase in O₃ levels, but an apparent adaptation effect with continued high O₃ exposures.

Pacini and co-workers compared nasal mucosal cells taken by brushing from residents of Florence, Italy (a high O₃ area) versus rural residents of Sardinia.
### Table 3
**Observational studies of air quality and the upper airway**

<table>
<thead>
<tr>
<th>Exposure: Endpoint</th>
<th>Observation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Meteorologic conditions</strong></td>
<td>Nasal symptoms</td>
<td>Symptoms in nonallergic rhinitic subjects varied with minimum daytime temperature, relative humidity, and air pollutant levels</td>
</tr>
<tr>
<td></td>
<td>Clinic visits for NAR</td>
<td>Unscheduled clinic visits for NAR increased with diurnal temperature variation, cold/dry weather, and with photochemical oxidants</td>
</tr>
<tr>
<td><strong>Ambient air pollutants</strong></td>
<td>Nasal biopsy</td>
<td>Squamous metaplasia comparing Mexico City versus rural residents</td>
</tr>
<tr>
<td></td>
<td>Nasal biopsy</td>
<td>Short-term visitors to Mexico City developed nasal neutrophilia</td>
</tr>
<tr>
<td></td>
<td>Nasal biopsy</td>
<td>Children from Mexico City versus unpolulated area showed squamous metaplasia, ciliary disorientation, intraepithelial exudate</td>
</tr>
<tr>
<td></td>
<td>Nasal symptoms and biopsy</td>
<td>Children from Mexico City versus unpolulated area reported greater nasal symptoms and showed squamous metaplasia, neutrophilia, p53 expression</td>
</tr>
<tr>
<td></td>
<td>Nasal lavage</td>
<td>Austrian school children underwent serial nasal lavage during air pollution season. An increase in WBC count and ECP concentration was apparent with increasing O₃ (early season only)</td>
</tr>
<tr>
<td></td>
<td>Nasal brushings</td>
<td>Adults from Florence, Italy (high O₃) versus Sardinia (low O₃) showed more DNA damage</td>
</tr>
<tr>
<td><strong>Indoor air pollutants</strong></td>
<td>Acoustic rhinometry; nasal lavage</td>
<td>Cross-sectional study of school personnel in which nasal patency, nasal ECP and lysozyme levels varied by building characteristic</td>
</tr>
<tr>
<td></td>
<td>Nasal symptoms</td>
<td>Individuals living in houses with elevated levels of the MVOC, 1-octen-3-ol, had higher rates of eye, nose and throat irritation</td>
</tr>
</tbody>
</table>

*Abbreviations:* ECP, eosinophilic cationic protein; IL, interleukin; MVOC, volatile organic compounds of microbial origin; NAR, nonallergic rhinitis; NO, nitrous oxide; TNF, tumor necrosis factor; WBC, white blood cell.

They found greater levels of DNA damage and more inflammatory changes among cytologic specimens from the Florence residents than from the rural Sardinians.

**Indoor air quality**

Studies of indoor air quality documenting nonallergic upper airway responses are quite numerous. We discuss a few representative studies.

Walinder and colleagues\(^4\) studied 234 primary school employees from 12 randomly selected Swedish schools. Health history was obtained by structured interview, and nasal symptoms documented using a self-administered questionnaire. Environmental measures included indoor temperature and concentrations of carbon dioxide, nitrogen dioxide, formaldehyde and other volatile organic compounds (VOCs), and dust. Acoustic rhinometry was performed after at least 1 hour of building occupancy. Nasal lavage fluid was analyzed for eosinophilic cationic protein, lysozyme, myeloperoxidase, and albumin. Symptomatically, self-reported nasal obstruction was related to ventilation type (mechanical vs natural), as well as dust concentrations. On acoustic rhinometry, nasal cross-sectional area was reduced as a function of dust concentrations, formaldehyde levels, the presence of polyvinyl chloride flooring, and the use of mechanical (vs natural) ventilation. On nasal lavage, lysozyme levels were higher with mechanical ventilation and wet mopping of floors whereas eosinophilic cationic protein levels were higher with decrease frequency of floor cleaning and with increasing levels of formaldehyde and nitrogen dioxide.

Araki and colleagues\(^4\) studied the occupants of 182 single family dwellings in Japan, performing indoor air analyses for VOCs, including those of microbial origin. Among the approximately 5% of respondents who reported home-related mucous membrane symptoms (eye, nose, and throat irritation), a significant relationship emerged between mucous membrane symptoms and indoor air concentrations of the VOCs of microbial origin [1-octen-3-ol] and [2-pentanol].

**Intervention studies**

Two studies were identified in which the effects of various interventions were evaluated on nonallergic mediated nasal symptoms or pathology. In one, atopic asthmatic children in Mexico City exposed to urban air pollution (as discussed) were given either antioxidant dietary supplements (vitamins C and E) or placebo, and concentrations of cytokines (interleukin [IL]-6 and IL-8) and antioxidants (glutathione and uric acid) in nasal lavage fluid were evaluated. The antioxidant-treated group showed significantly lower levels of IL-6 (and borderline lower levels of IL-8) during high-O\(_3\) days compared with placebo-treated children.\(^4\)

The second interventional study involved office workers who reported mucous membrane irritation at work. Their offices were subjected to either comprehensive or superficial (sham) cleaning on a blinded basis, resulting in significant reductions in airborne dust levels in the former group. Both subjective irritation and objective airway patency (by acoustic rhinometry) were recorded. The active intervention group reported a significant reduction in upper airway irritation symptoms after the intervention, as well as an increase in nasal patency.\(^4\)

**Controlled Human Exposure Studies**

A number of studies have examined subjective and/or objective nasal responses to environmental incitants in controlled human exposure protocols (Table 4). Although CDA provocation constitutes the dominant provocation paradigm for experimental
## Table 4
Controlled human exposure studies of nonallergic stimuli in the upper airway

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>Nasal Patency</th>
<th>Nasal Lavage</th>
<th>Mucoiliary Clearance</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetic acid</td>
<td>↑ $R_{nasal}$</td>
<td>—</td>
<td>—</td>
<td>Shusterman et al,72 2005</td>
</tr>
<tr>
<td>Ammonia</td>
<td>↑ $R_{nasal}$</td>
<td>—</td>
<td>—</td>
<td>McLean et al,61 1979</td>
</tr>
<tr>
<td>Barometric pressure</td>
<td>↓ PiF vs PiFo</td>
<td>—</td>
<td>—</td>
<td>Barry et al,46 2002</td>
</tr>
<tr>
<td>Carbonless copy paper</td>
<td>↑ $R_{nasal}$</td>
<td>—</td>
<td>—</td>
<td>Morgan &amp; Camp,73 1986</td>
</tr>
<tr>
<td>Chlorine gas</td>
<td>↑ $R_{nasal}$</td>
<td>NC tryptase, neuropeptides</td>
<td>—</td>
<td>Shusterman et al,62 1998; Shusterman,18 2002; Shusterman et al,63 2003; Shusterman et al,65 2003; Shusterman et al,66 2004</td>
</tr>
<tr>
<td>Environmental tobacco smoke</td>
<td>↑ $R_{nasal}$</td>
<td>NC histamine, albumin, kinins</td>
<td>↓ Clearance</td>
<td>Bascom et al,49 1991</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nowak et al,51 1997</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Schick et al,53 2013</td>
</tr>
<tr>
<td>Ozone</td>
<td>↑ PMNs</td>
<td>—</td>
<td>—</td>
<td>Graham et al,69 1988</td>
</tr>
<tr>
<td></td>
<td>↑ PMNs</td>
<td>—</td>
<td>—</td>
<td>Graham and Koren,70 1990</td>
</tr>
<tr>
<td></td>
<td>↑ PMNs, IL-8</td>
<td>—</td>
<td>—</td>
<td>McBride et al,71 1994</td>
</tr>
<tr>
<td>Sulfur dioxide</td>
<td>↑ $R_{nasal}$</td>
<td>—</td>
<td>↓ Clearance</td>
<td>Andersen et al,68 1974</td>
</tr>
<tr>
<td></td>
<td>NC $R_{nasal}$</td>
<td>—</td>
<td>—</td>
<td>Tam et al,67 1988</td>
</tr>
<tr>
<td>VOCs</td>
<td>↓ NV</td>
<td>—</td>
<td>—</td>
<td>Kjaergaard et al,54 1995</td>
</tr>
<tr>
<td></td>
<td>↑ PMNs</td>
<td>—</td>
<td>—</td>
<td>Koren et al,56 1992</td>
</tr>
<tr>
<td></td>
<td>↑ Cytokines</td>
<td>NC Clearance</td>
<td>—</td>
<td>Muttray et al,57 1999</td>
</tr>
<tr>
<td></td>
<td>NC Cytokines</td>
<td>↓ Clearance</td>
<td>—</td>
<td>Muttray et al,58 2002</td>
</tr>
<tr>
<td></td>
<td>↑ Cytokines</td>
<td>NC clearance</td>
<td>—</td>
<td>Mann et al,59 2002</td>
</tr>
</tbody>
</table>

**Abbreviations:** ↑, increased; ↓, decreased; NC, no change; NV, nasal volume (by acoustic rhinometry); PiF, nasal peak inspiratory flow; PiFo, oral peak inspiratory flow; PMNs, polymorphonuclear leukocytes; $R_{nasal}$, nasal airway resistance (by rhinomanometry); VOC, volatile organic compounds.

*a* Allergic rhinitic subjects only.

*b* Historically sensitive subjects only.

physical triggering in NAR, inhaled chemical irritants have also been used to document nonspecific nasal hyperreactivity in both NAR and AR patients/research subjects.

**PHYSICAL INCITANTS**

*Cold, Dry Air*

The CDA challenge has been used as the sine qua non of provocation agents in idiopathic NAR, and has been applied in a variety of study designs. These include clinical diagnosis/classification (including comparisons with methacholine or histamine challenge), pathophysiologic studies, and to monitor the therapeutic response to pharmacologic or surgical interventions. Typical endpoints include symptom ratings, weight of nasal secretions, and nasal patency. Because the volume of literature on this topic could justify a separate review article, only a few representative CDA studies are reviewed herein.

Braat and colleagues compared CDA challenge with histamine challenge with respect to their ability discriminate NAR subjects \( n = 16 \) from NR controls \( n = 7 \). Study endpoints included decreased nasal patency (by anterior rhinomanometry), weight of secretions, and number of sneezes. In a progressive challenge protocol, the investigators found both methods to be highly sensitive in identifying NAR subjects, but only CDA specific for NAR.

In an attempt to identify phenotypic subsets of NAR patients, Shusterman and Tilles compared the response to CDA challenge in 10 subjects who reported predominantly physical symptom triggers, 4 NAR subjects with predominantly chemical triggers, and 10 NR, nonatopic controls (NR). In the initial protocol, as few as 1 of 5 self-identified physical triggers classified a subject as NAR with physical symptom triggers, whereas at least 2 of 5 chemical triggers were required to qualify as NAR with predominantly chemical triggers. The 2 NAR subgroups combined showed significantly greater nasal obstruction after the CDA challenge than did the NR controls, but only after the definition of NAR with physical symptom triggers was modified, on a post hoc basis, to require 2 reported physical triggers \((P < .05)\). Across subjects, a positive trend was observed in degree of post-CDA nasal obstruction as a function of the number of self-reported physical triggers \((P < .05)\). Subjectively, self-reported nasal congestion after exposure was significantly greater in subjects with NAR with physical symptom triggers than in the other 2 subgroups.

Kim and colleagues compared the response to CDA challenge between 21 normal controls, 24 AR patients, and 32 NAR patients. Subjects were stratified, before the challenge, into “hyperreactive” and “nonhyperreactive” subgroups based on their self-reported reactivity to cold air. Symptom scores by visual analog scales and nasal volumes by acoustic rhinometry were evaluated before and after the CDA challenge, and the degree of CDA-induced rhinorrhea assessed by weight of nasal secretions after the exposure. Both AR and NAR groups exhibited significantly greater increases in symptoms and nasal secretions—and decreases in nasal volume—after the CDA challenge than did normal controls. In addition, objective findings (ie, nasal patency and secretions) were more prominent among subjects with a self-reported history of nasal hyperreactivity.

Bernstein and colleagues evaluated 37 NAR subjects with CDA challenge (and with temperature change alone) in a multiseat environmental chamber. Acoustic rhinometry was used to evaluate nasal patency, weight of nasal secretions was the index of rhinorrhea, and subjective congestion, rhinorrhea, and postnasal drip were self-rated. With CDA challenge, 25 of 37 subjects met preset criteria for a symptomatic response,
and 20 of 37 met rhinometric criteria (i.e., demonstrated a $>10\%$ decrease in nasal patency). The observed increase in rhinorrhea was highest for CDA and the cold air phase of the temperature change protocol. The study was interpreted as a proof-of-concept for the feasibility of using a multi-seat environmental challenge chamber to simultaneously elicit weather-induced symptoms and physiologic changes in multiple NAR patients.

**Barometric Pressure and Altitude**

Using a hypobaric chamber, Barry and colleagues$^{48}$ simulated ascent to more than 8000 m while maintaining constant temperature and humidity, measuring both nasal and oral peak inspiratory flow at the equivalent of 0, 5000, and 8000 m altitude. Although both peak inspiratory flows increased with decreasing barometric pressure, the increase in nasal peak inspiratory flow was considerably less than that of oral peak inspiratory flow, which was interpreted as showing a relative airflow limitation in the upper versus lower airway.

**CHEMICAL INCITANTS**

**Environmental Tobacco Smoke**

Bascom and colleagues$^{49}$ exposed 21 adult subjects to sidestream tobacco smoke (STS) for 15 minutes, asking subjects to rate symptoms before and after exposure. The surrogate measure of exposure was a carbon monoxide concentration of 45 ppm (equivalent to a smoky bar). The subjects were subdivided into 10 who previously reported being sensitive to environmental tobacco smoke (ETS-S) and 11 historically nonsensitive (ETS-NS), with the majority of the ETS-S subjects being atopic and the majority of the ETS-NS subjects being nonatopic. ETS-S subjects reported significantly more nose and throat irritation than ETS-NS subjects. Furthermore, on posterior rhinomanometry the ETS-S group showed significant increases in nasal airway resistance when compared with the ETS-NS group. The exposures were repeated subsequently and followed by nasal lavage rather than rhinomanometry. Neither subgroup showed evidence of an IgE-mediated reaction, as evidenced by a lack of significant alterations in nasal lavage fluid histamine, kinins, TAME-esterase, or albumin after exposure.

The same group examined the endpoint of nasal mucociliary clearance after STS exposure. 99mTc-sulfur colloid was aerosolized into the nose after STS and clean air exposures, and clearance was measured by scintillation counter and compared between the 2 exposure conditions. One-half of the subjects showed increased clearance, 25% showed no change, and 25% showed decreased clearance after STS exposure. The group with decreased clearance all gave a history of ETS–related rhinitis symptoms.$^{50}$

Nowak and colleagues$^{51}$ performed nasal lavage on 10 mild asthmatics before and after exposure to STS at 22 ppm carbon monoxide, analyzing for histamine, albumin, eosinophil cationic protein, myeloperoxidase, hyaluronic acid, and tryptase. Bronchoscopy was also performed the morning after exposure. Although there was an increase in respiratory symptoms after exposure, no systematic changes were observed in spirometry, nasal lavage fluid, or bronchoalveolar lavage fluid.

Junker and colleagues$^{52}$ exposed 24 subjects to STS at variable concentrations. They found a dose–response for self-rated odor intensity, eye irritation, and annoyance as a function of airborne particle, polycyclic aromatic hydrocarbon, and VOC concentrations. Subjective nasal irritation, on the other hand, was related only to particle concentration. Neither breathing pattern nor eye blink rate (a measure of eye irritation) varied significantly with STS concentration. The mean threshold for
STS odor detection among these subjects corresponded with a PM (Particulate Matter) concentration of approximately 0.6 to 1.4 μg/m³.

Schick and colleagues studied 26 healthy nonsmokers (10 nonatopic without rhinitis, 7 atopic without rhinitis, 7 atopic with rhinitis, and 2 nonatopic with rhinitis) in a STS provocation study. Subjective nasal symptoms were assessed by questionnaire, objective nasal congestion by active anterior rhinomanometry, and nasal nitric oxide concentrations were determined before and after exposure. Exposure to experimentally aged cigarette smoke (at 1 mg/m³ particulate concentration/14 ppm carbon monoxide) for 30 minutes was compared with exposure to clean air on a separate day. Overall, exposure to SHS increased nasal resistance in healthy nonsmokers (P<.05). The increase in nasal resistance was most pronounced in rhinitis subjects. No systematic changes in nasal nitric oxide were observed as a function of exposure in any of the subgroups.

**Volatile Organic Compounds**

Kjaergaard and colleagues exposed 18 each “hay fever” and normal subjects to a mixture of 22 different VOCs at a total concentration of 20 mg/m³ for 4 hours. Exposure to the clean air control condition occurred on a separate day. Hayfever subjects showed more pronounced increases in self-reported eye, nose, and throat irritation over the course of the exposure than did nonallergic subjects. However, rhinitis and NR subjects showed equivalent exposure-related decreases in nasal volume on AR.

Hudnell and colleagues compared the response of adult male volunteers exposed to the same mixture of 22 VOCs at a total concentration of 20 mg/m³ over a 2.75-hour period, and found increasing self-reported eye and throat irritation, headache, and drowsiness, whereas odor ratings decreased during exposure (consistent with odor adaptation). In the same laboratory, Koren and colleagues conducted identical VOC exposures over 4 hours, obtaining nasal lavage fluid before and after exposure. Investigators found increases in polymorphonuclear leukocytes (PMNs) in nasal lavage fluid both immediately after exposure and at 18 hours after exposure.

Muttray and colleagues exposed 12 healthy subjects to 1,1,1-trichloroethane (TCA) at 20 and 200 ppm for 4 hours, assessing nasal mucociliary function (by saccharine transit time) and sampling nasal secretions 20 minutes after exposure. Cytokines, including IL-1B, IL-6, and IL-8 were analyzed in nasal secretions, and ciliary beat frequency determined on sampled cells studied ex vivo. Although neither measure of mucociliary function was significantly altered, all 3 cytokines were elevated in concentration after exposure.

The same laboratory group studied 19 healthy volunteers exposed to 0 and 200 ppm methyl ethyl ketone, again analyzing secretions for cytokines and documenting mucociliary function (saccharine transit time). In this study, mucociliary transport time was increased significantly after exposure, but cytokines showed no changes (the inverse of the pattern observed in their TCA study). Also from this group, Mann and colleagues studied the response of 12 healthy subjects to 20 and 200 ppm of methanol, examining cytokines, mucociliary clearance, and ciliary beat frequency of sampled nasal epithelial cells. Both IL1B and IL-8 concentrations were increased after exposure, whereas IL-6 and prostaglandin E2 were unchanged. However, neither measure of mucociliary function was altered by the exposure.

Andersen and colleagues studied nasal airway resistance and mucociliary clearance during 6-hour exposures to 10, 40, or 100 ppm of toluene vapor. No significant exposure-related changes were noted in either physiologic parameter.
**Ammonia**

McLean and colleagues measured nasal airway resistance among 33 SAR and NR subjects before and after exposure to ammonia (100 ppm times 5 seconds per nostril). Exposures were repeated at 15-minute intervals, with successively longer durations of exposure (10, 15, and 20 seconds). The mean nasal airway resistance increased after NH₃ exposures, and a dose–response was evident for exposure duration; however, no difference was apparent between subgroups by rhinitis status. Pretreatment with topical atropine, but not chlorpheniramine, inhibited ammonia-induced nasal airflow obstruction.

**Chlorine**

Shusterman and colleagues compared the response of 8 SAR and 8 NR subjects, exposed for 15 minutes to chlorine (Cl₂) at 0.5 ppm, with control (clean air) exposures occurring either a week before or after the irritant exposure (in counterbalanced order). SAR subjects were tested out of season. Endpoints included self-rated nasal symptoms and nasal airway resistance by active posterior rhinomanometry. After chlorine provocation, significant increases in self-rated nasal irritation and increases in nasal airway resistance were documented in SAR subjects only. In a larger (n = 60) sample of subjects stratified by age, sex, and allergy status, the same group found that both AR and age (older subjects) predicted an augmented congestive response to 1.0 ppm Cl₂ gas.

This Cl₂ exposure paradigm was applied by Shusterman and colleagues to explore underlying mechanism(s) of irritant-induced nasal airway obstruction. In the first pathophysiological study, subjects were pretreated with ipratropium bromide nasal spray on a double-blinded, placebo-controlled basis before Cl₂ or fresh air exposure. Differential Cl₂-induced nasal obstruction by rhinitis status was not affected by ipratropium bromide pretreatment, suggesting that cholinergic reflexes were not responsible for the observed response. In a separate experiment, nasal lavage fluid was analyzed for evidence of mast cell degranulation (tryptase) and neuropeptide release (SP, calcitonin gene-related peptide, VIP, and NPY), but neither set of markers were systematically affected by exposure. Thus, in this series of experiments no evidence was found that mast cell degranulation, neuropeptide release, or cholinergic reflexes were responsible for chlorine’s effect on nasal patency.

**Sulfur Dioxide**

Tam and colleagues studied 22 AR subjects exposed by nasal mask to 4 ppm of sulfur dioxide (SO₂) for 10 minutes, as well as 8 subjects with combined asthma and rhinitis exposed to 1 to 2 ppm SO₂ by mouthpiece. There were no exposure-related changes in either nasal airway resistance or nasal symptoms. These results are in contrast with an earlier study by Andersen and colleagues, which documented SO₂-induced nasal airflow obstruction, as well as alterations in nasal mucociliary clearance.

**Ozone**

Graham and colleagues exposed 20 subjects to filtered air and 19 subjects to 0.5 ppm O₃ for 4 hours on 2 successive days. Subjects underwent nasal lavage before exposure on both days, as well as immediately after exposure on day 1 and 22 hours after exposure on day 2. The O₃-exposed group showed increased numbers of PMNs in nasal lavage fluid in all postexposure samples, including an elevated baseline before the second day’s exposure.
Graham and Koren\textsuperscript{70} compared the upper and lower respiratory tract responses of 10 nonsmoking subjects without asthma exposed to 0.4 ppm O\textsubscript{3} for 2 hours with exercise. Parallel increases in PMNs and albumin were apparent in nasal lavage and bronchoalveolar lavage fluids at 18 hours after exposure, in addition to an early increase in PMNs documented on nasal lavage.\textsuperscript{70}

McBride and colleagues\textsuperscript{71} exposed 10 atopic asthmatic subjects to 0, 0.12, and 0.24 ppm O\textsubscript{3} for 90 minutes during intermittent exercise. Nasal lavage and nasal work of breathing were obtained before exposure, immediately after exposure, and at 6 and 24 hours after exposure. At the higher exposure level (0.24 ppm), a significant increase in nasal lavage white blood cell count was observed at the earliest and latest postexposure sampling time, but not at 6 hours. In addition, a significant correlation was found between nasal lavage white blood cell count and IL-8 levels. However, no changes in either nasal work of breathing or pulmonary function were observed after exposure.

**Acetic Acid**

Shusterman and colleagues\textsuperscript{72} compared the responses of 8 SAR and 8 NR subjects exposed to acetic acid vapor (at 15 ppm) versus filtered air for 15 minutes on separate days. The AR subjects showed significant increases in nasal airway resistance compared with NR, with responses evident both immediately after exposure and at 15 minutes after exposure.

**Carbonless Copy Paper**

Morgan and Camp\textsuperscript{73} studied 30 workers with self-reported skin and/or respiratory sensitivity to carbonless copy paper. Air was passed through shredded carbonless copy paper or bond paper and supplied to the breathing zone of subjects. Mean nasal airway resistance by rhinomanometry increased by 34\% after carbonless copy paper exposure compared with 8\% after bond paper exposure. However, symptoms did not correlate with the magnitude of nasal airway resistance changes.\textsuperscript{73}

**Paper Dust**

Theander and Bender\textsuperscript{74} studied 15 NAR subjects who reported nasal symptoms to newspapers, and compared them with 6 healthy controls. Subjects inhaled either vapors from printing ink or paper dust, and then rated nasal symptoms on visual analog scales, as well as having their nasal airway resistance measured by anterior rhinomanometry. The NAR subjects reported significantly greater symptoms than did controls after paper dust, but not ink vapor, exposure. However, neither group showed significant changes in nasal airway resistance.\textsuperscript{74}

**Dry Powder Mannitol**

Although more properly classified as a pharmacologic than an environmental exposure study, Koskela and colleagues\textsuperscript{75} study of dry powder mannitol exposure (a noxious, hyperosmolar stimulus) is relevant in the context of this discussion. Ten healthy controls, 11 with SAR (studied out of season while asymptomatic), and 9 symptomatic rhinitis patients (all but one with perennial AR) underwent nasal challenge. Nasal symptoms, nasal peak inspiratory flow, and nasal lavage was performed before and after dry powder mannitol or sham exposure, with the order of exposure randomized on separate days. All patients reported an immediate burning sensation of varying severity, and both AR subgroups showed increases in nasal lavage 15-hydroxyeicosatetraenoic acid (15-HETE; a marker of epithelial cell activation). However, only the AR patients with active symptoms experienced a decrease in nasal
peak inspiratory flow (i.e., nasally congested). No increases in nasal lavage substance P were observed, although a third of the AR patients showed exposure-related increases in mast cell tryptase (a marker of mast cell degranulation that, however, did not predict the severity of nasal blockage).

**MECHANISM(S) UNDERLYING CHEMICAL IRRITANT-INDUCED NASAL REFLEXES**

Potential reflex mechanisms for irritant-induced rhinorrhea and nasal obstruction are diagrammed in Fig. 4. Reading from “right to left,” rhinorrhea generally reflects a glandular response, although some contribution may come from plasma extravasation. Nasal “congestion” (obstruction), on the other hand, involves primarily vasodilation of large capacitance vessels, again with a secondary contribution by extravasated plasma.

Moving “upstream” with respect to reflex mechanisms, rhinorrhea induced by both cold air and capsaicin can occur contralaterally after unilateral nasal stimulation, and can be inhibited by topical cholinergic blockers, thereby implicating a central (parasympathetic) reflex mechanism affecting submucosal glands. Moving upstream with respect to reflex mechanisms, rhinorrhea induced by both cold air— or capsaicin—induced rhinorrhea—are characterized by the predominant nasal lavage proteins being glandular products (i.e., lactoferrin and lysozyme). By contrast, in nasal lavage fluids obtained after mast cell degranulation (i.e., after an allergic reaction), the predominant proteins are derived from plasma (i.e., albumin and various Igs) along with histamine and/or tryptase. This matrix of physiologic endpoints, biochemical markers, and pharmacologic blockers has been applied, to a limited extent, to the question of chemical irritant-induced nasal congestion, for which the results of relevant provocation experiments appear in Table 4.

A brief summary of biochemical marker/pharmacologic blocker studies is as follows.

- In 3 separate experiments, irritant-induced nasal obstruction (provoked by STS, chlorine gas, or dry powder mannitol) occurred in susceptible individuals without consistent evidence in nasal lavage fluid of mast cell degranulation.49,65,75

- In one double-blinded, placebo-controlled, crossover study, pretreatment with a cholinergic blocker did not diminish the degree of Cl₂-induced nasal obstruction in susceptible individuals. However, in another (noncrossover) study, pretreatment with atropine did diminish ammonia-induced nasal obstruction.\textsuperscript{61}

- In two different studies (using either Cl₂ gas or dry powder mannitol as provocation agents), neither nasal lavage substance P nor other nasal lavage neuropeptides (calcitonin gene-related peptide, NPY, or VIP) were systematically altered in individuals who experienced irritant-induced nasal obstruction.\textsuperscript{66,75}

- One study (using dry powder mannitol provocation) examined 15-HETE, a biochemical marker of epithelial cell activation, and found significant increases in nasal lavage fluid concentrations among AR subjects, a subset of whom experienced objective irritant-induced nasal obstruction.\textsuperscript{75}

### Summary of mechanistic studies

- Acute irritant-induced nasal obstruction could potentially occur through mast cell degranulation, central neurogenic (eg, parasympathetic) reflexes, peripheral neurogenic (ie, “axon”) reflexes, or epithelial cell activation (see Fig. 4). Human studies evaluating these potential mechanisms have generally been either negative or have produced contradictory results. Early indications that epithelial cell activation may be an operative mechanism should be replicated using a wider range of provocation agents and in various subsets of susceptible individuals (ie, NAR; AR with nasal hyperreactivity).

- NAR patients, in general, have yet to be studied with chemical irritant provocation (other than with capsaicin or hypertonic saline). This constitutes a gap in the research literature.

### SUMMARY

Idiopathic NAR, because of its inconsistent association with mucosal inflammation, has been renamed by some as “nonallergic rhinopathy.” This condition has a slight female predominance, and tends to have its onset in adulthood. The clinical hallmark of this condition is nonspecific nasal hyperreactivity (ie, hyperresponsiveness to physical and chemical agents), although this phenotypic trait is also shared by many patients with AR. Cardinal symptoms of NAR—nasal hypersecretion and obstruction—have been explored mechanistically, but with varying degrees of success. Common triggers of NAR of environmental concern include cold/dry air, fragrance products, household cleaners, tobacco and wood smoke, vehicular exhaust, and industrial chemicals (vapors, gases, and particulate matter). Avoidance of these triggers can be challenging for some individuals, and as a consequence the condition has attracted significant attention in pharmaceutical circles.

Current controversies in idiopathic NAR include the role of sensory nerves, as nociceptive ion channel (eg, TRPV1, TRPA1) blockers increasingly become available, and as capsaicin desensitization trials continue to be conducted. Importantly, the advent of the competing diagnosis “local AR” calls into question the very classification of many patients labeled as having NAR, absent their having shown negative results on nasal allergen provocation testing and/or having proved refractory to conventional allergy medications.\textsuperscript{77} Amid all this uncertainty, what seems clear is that our clinical practice and mechanistic understanding regarding idiopathic NAR (or nonallergic rhinopathy) is likely to undergo dramatic changes over the next few decades.
REFERENCES


