

## Review of the Upper Airway, Including Olfaction, as Mediator of Symptoms

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The upper airway serves as air conditioner, filter, and warning device. Two neurological modalities, olfaction and trigeminal chemoreception, inform us of the chemical qualities of the air we breathe. A number of poorly understood conditions, including nonallergic rhinitis, irritant-induced rhinitis, odor-triggered asthma, odor-triggered panic attacks, chemical-induced olfactory dysfunction, and irritant-associated vocal cord dysfunction, involve induction of symptoms by odorant and/or irritant chemicals in the upper airway. This article is a summary of the knowledge and theories about these various conditions, and highlights those aspects of nasal anatomy, physiology, and pathophysiology relevant to their understanding. *Key words:* air pollutants, asthma, irritants, olfaction, panic disorder, rhinitis, trigeminal chemoreception, unexplained symptoms, vocal cord dysfunction. *Environ Health Perspect* 110(suppl 4):649–653 (2002). <http://ehpnet1.niehs.nih.gov/docs/2002/suppl-4/649-653shusterman/abstract.html>

The upper airway, including nasal cavity, pharynx, and larynx, is the gateway to the respiratory tract (Figure 1). In that role, it fulfills several functions, including air conditioning, filtering, sensation, and communication (Table 1). Adverse effects from air pollutants may affect the upper airway as the target or trigger other adaptations indirectly (Table 2). Central to the understanding of pollutant-related health effects is an appreciation of the anatomy and physiology of the upper respiratory tract.

Under most climatic conditions, inspired air is heated (to 37°C) and humidified (to near 100% relative humidity) in the upper airway (1). Filtration is accomplished mechanically by nasal vibrissae and by the process of impaction whereby large-diameter-inspired particles collide with the turbinates and are subsequently cleared by the mucociliary apparatus. In the case of aerosols carrying infectious agents, the mucosa produce both specific and nonspecific defenses, the former including secretory IgA and the latter including lactoferrin and lysozyme (2). Water-soluble irritants, including ammonia, chlorine, and various organic acids and aldehydes in cigarette smoke, readily dissolve in the mucous membrane layer of the cornea and upper airway (“scrubbing”), thus protecting the lower respiratory tract during nasal breathing (3). In this process the eyes, nose, and throat are irritated, serving as a warning to reduce exposure (Figure 2). Air pollutants vary in their relative irritant and odorant potencies, such that odor and irritation may be experienced singly or in combination, depending on the specific compound(s) involved, the exposure level(s), duration, and the sensory characteristics of the individual who is exposed (4,5).

In terms of sensation, the nasal cavity is innervated by two 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

irritation, also referred to as chemesthesis or the common chemical sense) (Figure 3). In addition, the glossopharyngeal and vagal nerves (cranial nerves IX and X) convey the sense of irritation for the hypopharynx and larynx. Just as our appreciation of foods involves a combination of the senses of taste, smell, and mucosal irritation, our appreciation of many inhaled compounds involves aspects of olfaction and trigeminal stimulation (6). The latter carries sensations ranging from freshness or tingling (e.g., in response to menthol) to burning or stinging (as elicited by ammonia or chlorine). Because the cornea, another structure vulnerable to environmental irritants, is also innervated by the trigeminal nerve, eye irritation is often grouped with upper respiratory tract irritation for purposes of discussion. Specialized psychophysical methods have been developed to quantitate both threshold and suprathreshold perceptions in olfaction and chemesthesis (7,8). These techniques are important adjuncts to studying chemically mediated symptoms in both clinical and experimental settings.

### The Upper Airway as a Target

#### Nonallergic Rhinitis

The relationship between irritant rhinitis and other types of nonallergic rhinitis is not fully defined. Despite inconsistent terminology (so-called vasomotor rhinitis, noneosinophilic nonallergic rhinitis, and nonallergic, noninfectious perennial rhinitis), all include in their description an exaggerated reactivity to common physical and chemical stimuli. Patients frequently report congestion or rhinorrhea in response to changes in air temperature or humidity, exposure to bright lights, exercise, consumption of alcohol, or exposure to perfumes, household cleaning products, or environmental tobacco smoke (9). Pharmacologic challenge (with methacholine or histamine), as well as challenge with cold, dry air, have

been used to demonstrate differences in responsiveness among various rhinitic subgroups and controls (10–12). Unfortunately, the subtypes of nonallergic rhinitis, as well as the concept of nasal hyperreactivity, still lack consensus definitions.

Limited insight into nonallergic response mechanisms does exist, however. In both experimental animals and humans, activation of upper respiratory tract irritant receptors may trigger a variety of airway reflexes, including sneezing, rhinorrhea, nasal congestion, cough, laryngeal constriction, and bronchoconstriction (13). Although most of these reflexes have potential protective functions, they may be troublesome if present in an exaggerated form. Theories explaining augmented nasal reflex symptoms in nonallergic rhinitis include sensory hyperesthesia, cholinergic hyperreactivity, and sympathetic hyporeactivity. Limited data distinguish among these alternatives; however, based upon challenge studies and the use of cholinergic blockers, the parasympathetic nervous system appears to be involved in at least the secretory component of this disorder (14). Local (axon) reflexes, involving release of substance P and other neuropeptides, may also be operative (15).

#### Irritant-Induced Rhinitis

Also relevant in this context is the hypothesis that a one-time exposure to an irritant can initiate irritant rhinitis, similar to the situation for irritant-induced asthma, or reactive airways dysfunction syndrome (RADS) (16). One investigator suggested that irritant-induced rhinitis be termed reactive upper airways dysfunction syndrome or RUDS (17). Biopsies of the nasal mucosa among individuals acutely exposed to irritants have reportedly shown epithelial desquamation, defective epithelial cell junctions, and increased numbers of nerve fibers, although patients and controls did not differ in staining for neuropeptides (18). Individuals with a history of persistent upper airway symptoms after irritant exposures who

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have also complained of multisystem reactivity to low-level chemical exposures have been labeled “chemically sensitive,” and it has been suggested that they have either increased levels of circulating neuropeptides (19) or have undergone “neurogenic switching,” in which airway inflammation encourages inflammation in other organ systems (20). Unfortunately, the number of testable hypotheses that have emerged from this literature is scant, and it is unclear that the individuals in these case series have clinical presentations beyond the scope of more conventional diagnoses, including the more descriptive “irritant rhinitis” (21).

**Irritant-Associated Vocal Cord Dysfunction**

Vocal cord dysfunction (VCD), an episodic disorder also referred to as “paradoxical vocal cord motion,” can produce a variety of symptoms, including throat tightness (globus),

stridor, and laryngeal wheezing (often mistaken for asthma). The hallmark of the condition is the finding on laryngoscopy of inappropriate adduction of the vocal cords (folds) during inspiration (Figure 4). In addition to an oft-cited connection with psychological factors, there is increasing evidence that inflammatory conditions, including both rhinitis/sinusitis with chronic postnasal drip as well as gastroesophageal reflux disease (GERD), can initiate or exacerbate this condition (22). Recent work suggests that some individuals may also manifest VCD symptoms after exposure to airborne irritants as an initiating and/or triggering event (so-called irritant-associated vocal cord dysfunction) (23).

**Chemically Induced Olfactory Dysfunction**

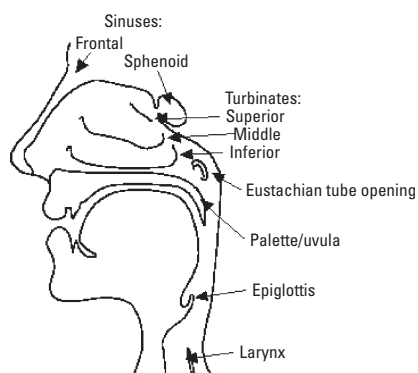
Workplace exposure to a number of irritant chemicals has been associated with subjective and objective olfactory loss. Among these agents are cadmium (battery workers and braziers), hydrocarbons (paint formulators and tank cleaners), and ammonia and sulfuric acid (chemical plant workers). Because most affected occupational cohorts have been studied cross-sectionally only, little can be said about the natural history of such impairment (24). In addition both hydrogen sulfide and the various mercaptans can produce profound olfactory fatigue of a transient nature.

Potential mechanisms of chemically induced olfactory impairment include direct toxicity to the olfactory epithelium, injury to the central nervous system proper, and impaired delivery of odorants to the olfactory epithelium (due to congestion and high-grade airflow obstruction). Olfactory loss can have important health implications, including impaired ability to recognize food spoilage, failure to detect gas leaks, and impaired ability to detect respirator cartridge breakthrough (for workers required to wear respirators) (25). Distorted olfactory perception (dysosmia), which can occur after either viral or chemical insult, may produce not only negative hedonic responses but also frank alarm and secondary autonomic activation in some individuals (see discussion of multiple chemical sensitivities below).

**The Upper Airway as Mediator of Symptoms**

**Odor-Triggered Asthma**

Asthma is a medical condition in which individuals are widely believed to be more sensitive to odors (26–30). Shim and Williams found that 90% of a group of 60 asthmatic individuals surveyed reported exacerbations of



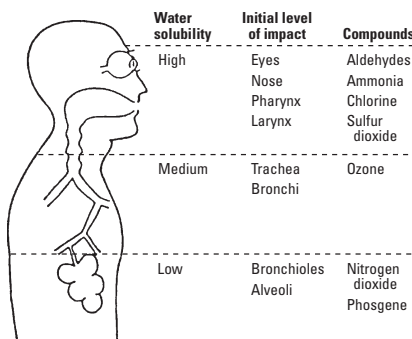
**Figure 1.** Principal anatomical features of the upper respiratory tract.

**Table 1.** Functions of the upper airway.

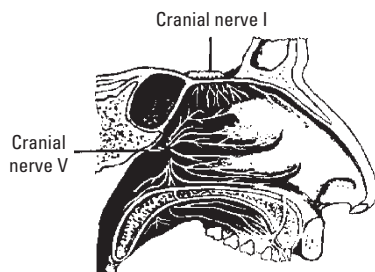
| General          | Specific  |
|------------------|---|
| Air conditioning | Heating<br>Humidification   |
| Air filtration   | Microbes (inactivation)<br>Particulates (mucociliary clearance)<br>Vapors (scrubbing) |
| Sensation        | Olfaction (odor perception)<br>Chemesthesis (irritant perception)                     |
| Communication    | Hearing (pressure regulation of the middle ear)<br>Speech (phonation)                 |

**Table 2.** Role of upper airway in symptom complexes.

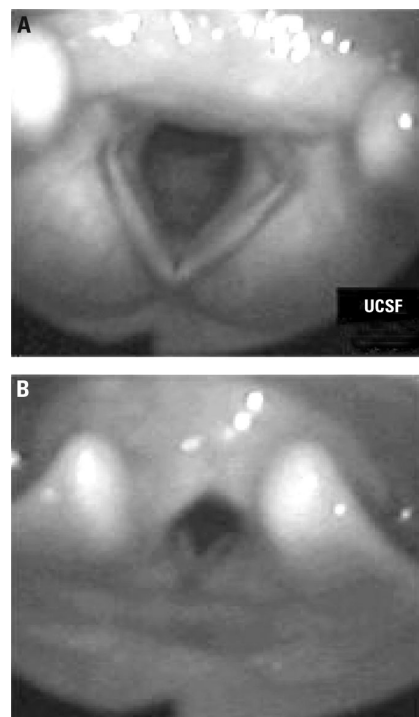
| Condition                                | Target | Mediator |
|--|--------|----------|
| Nonallergic rhinitis                     | X      |          |
| Irritant-induced rhinitis                | X      |          |
| Chemically induced olfactory dysfunction | X      |          |
| Irritant-induced vocal cord dysfunction  | X      |          |
| Odor-triggered asthma                    |        | X        |
| Odor-triggered panic attacks             |        | X        |



**Figure 2.** Effect of water solubility of a gas or vapor on initial site of mucous membrane irritation. Adapted from U.S. DHHS (3).



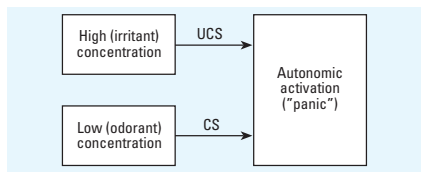
**Figure 3.** Anatomical distribution of the first (olfactory) and fifth (trigeminal) cranial nerves within the upper airway.



**Figure 4.** Laryngoscopic images of vocal cords (folds) during expiration (A) and inspiration (B) in a patient with irritant-associated vocal cord dysfunction. Note paradoxical adduction (closure) of cords during inspiration. Images courtesy of C. Gress, University of California, San Francisco/Mt. Zion Voice Center.

asthma related to odorant exposures, and nearly 40% had visited emergency departments after such incidents. One quarter of respondents also reported nasal symptoms (congestion, sneezing) during odorant exposures. In this same publication (29), the authors reported on a small-scale experiment in which four asthmatic individuals were exposed to aerosolized cologne for 10 min; there were significant acute drops in forced expiratory volume in 1 sec (FEV<sub>1</sub>) in all subjects. On repeat testing, pretreatment with placebo (saline) had no effect on these pulmonary function changes, whereas pretreatment with atropine or metaproteronol either blunted them or prevented them entirely. Use of a nose clip prevented pulmonary function changes in only one of three subjects tested (29). The finding of significant acute pulmonary function changes despite the use of a nose clip implies a direct, possibly irritant, action on the bronchial epithelium by the test agent (cologne) used. Some of the odorants listed in the survey (tobacco smoke, household cleaning products) clearly had irritant properties as well.

Along this same line of investigation, Kumar and colleagues (30) exposed 29 asthmatic individuals and 13 normal controls to filter-paper strips containing *a*) saline placebo, *b*) 70% isopropyl alcohol (IPA), or *c*) a commercial perfume, as well as to strips from a magazine containing that same perfume. Asthmatic individuals varied in their disease severity from mild to severe, and skin-prick testing confirmed a lack of immunologic reaction to the perfume employed in all but three of the experimental subjects. For both delivery modes, the perfume exposure produced significant declines in FEV<sub>1</sub> in the asthmatic group compared with that in controls, with smaller changes being documented after IPA exposure alone. One in five asthmatic individuals complained of chest tightness, wheezing, and rhinitis after perfume challenge, whereas none complained of such symptoms after IPA exposure. Significantly, the magnitude of perfume-related pulmonary function decrements was related to the baseline severity of subjects' asthma (30).



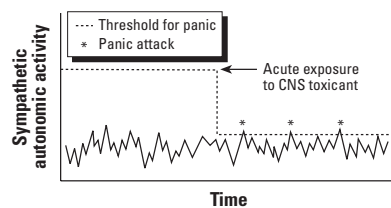
**Figure 5.** Model for respondent (Pavlovian) conditioning to compounds with both irritant and odorant properties. UCS, unconditioned stimulus; CS, conditioned stimulus. Reproduced from Shusterman and Dager (39) with permission from Hanley and Belfus Publishers.

These studies underscore the degree to which environmental stimuli, including those usually identified as odorants, may exacerbate asthma. Differentiation of odor-versus irritant-related changes in pulmonary function, however, may require special attention by researchers. Reference to animal experimental data in which respiratory behavior alterations can be seen in response to irritant exposure may provide ancillary information for selected chemical compounds of interest (31–34).

### Odor-Triggered Panic Attacks

Shusterman and colleagues (35) previously reported two cases of intolerance to specific odorants (industrial chemicals) that developed after a one-time overexposure involving significant respiratory tract irritation. In each case the worker tolerated the compound's odor prior to the incident but found him/herself experiencing symptoms of hyperventilation (air hunger, lightheadedness, acrodigital paresthesias, anxiety) upon exposure to the compound subsequent to the overexposure. In each case serious respiratory tract pathology was ruled out. A mechanism of respondent (Pavlovian) conditioning was postulated (Figure 5) (35). Similar cases had previously been labeled "atypical posttraumatic stress disorder" by Schottenfeld and Cullen (36), and an analogous mechanism was subsequently proposed for episodic "neurotoxic" symptoms (37).

Dager and colleagues (38) reported another series of patients in which individuals first showed paniclike symptoms when working with solvents in enclosed spaces. In contrast to the irritant-exposed patients, these individuals were hypothesized to have experienced a mild solvent narcosis, with a subsequent lowering of their threshold for a panic response (Figure 6). These cases (solvent related) and the above-described postirritant exposures were subsequently reviewed by Shusterman and Dager, who suggested the



**Figure 6.** Model for psychobiologic induction of panic attacks by weakly narcotic agents (e.g., solvent vapors). Dotted line represents threshold for panic, which is hypothesized to be altered by narcotic state. Once initial panic attack has occurred, this model postulates a perpetuation of lowered threshold, either by conditioning or by neural kindling. Reproduced from Shusterman and Dager (39) with permission from Hanley and Belfus Publishers.

uniform terminology of "odor-triggered panic attacks." This label was proposed for cases exhibiting episodic dyspnea coupled with central nervous system (CNS) and autonomic symptoms meeting the criteria for panic attacks, and occurring in response to perceived environmental odors, regardless of the prior exposure history (39).

Several recent studies have examined the potential contribution of olfaction and olfactory-related central nervous system reflexes in so-called multiple chemical sensitivities (MCS) or idiopathic environmental intolerance (IEI). Doty and colleagues (40) compared odor detection thresholds from 18 patients with a diagnosis of MCS versus a group of suitably matched controls and found no difference between the two groups (i.e., MCS patients were apparently hyper-reactors rather than hyperperceivers). In terms of defining these reactions, comparison of episodic symptoms reported in MCS/IEI and those reported in panic disorder shows considerable overlap (Table 3). In their original 1987 study, Dager et al. (38) conducted intravenous sodium lactate challenges on three patients with "panic disorder precipitated by exposure to organic solvents," and all three responded with typical panic symptoms.

More recently Binkley and Kutcher (41) studied five patients with a diagnosis of MCS and found that all met the DSM-IV criteria for panic disorder and also responded with paniclike symptoms to intravenous sodium lactate infusion. Lenzoff and Binkley challenged 15 MCS patients with identified trigger substances; 11 patients responded with acute hyperventilation, as evidenced by a fall in end-tidal CO<sub>2</sub> levels (42). Finally, Poonai and colleagues conducted CO<sub>2</sub> inhalation challenges on 36 subjects with IEI and 37 healthy controls (see accompanying article by Tarlo). The two groups differed significantly in their scores on the Anxiety Sensitivity Index (IEI subjects scoring higher), and significantly more IEI than control subjects reacted to CO<sub>2</sub> provocation with paniclike symptoms (71 vs. 26%; *p* < 0.001) (43).

Mechanistically, Wood reviewed the use of inhalants as conditioned and unconditioned

**Table 3.** Comparison of acute symptoms in MCS/IEI and panic disorder.

| Symptom                     | MCS/IEI <sup>a</sup> | Panic <sup>b</sup> |
|-----------------------------|----------------------|--------------------|
| Acute mental status changes | X                    | X                  |
| Lightheadedness             | X                    | X                  |
| Dyspnea/air hunger          | X                    | X                  |
| Paresthesias                | X                    | X                  |
| Palpitations                | X                    | X                  |
| Nausea                      | X                    | X                  |
| Sweating                    | X                    | X                  |
| Headache                    | X                    | –                  |

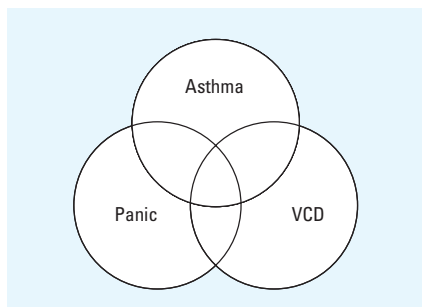
<sup>a</sup>Data from Cone et al. (55). <sup>b</sup>Data from APA (56).



stimuli in animal behavior studies (44) and pointed out that as early as the 1920s and 1930s, odorants were studied as conditioned stimuli (45,46). Unconditioned, irritant-related changes in respiratory behavior have been documented in both experimental animals (47) and humans (48–50). Of relevance here, recent work by Van den Berg's group in Belgium has examined learning paradigms in which subirritant levels of CO<sub>2</sub> are used as an unconditioned stimulus for hyperventilation, and various inhaled odorants (again, at nominally subirritant levels) as conditioned stimuli. In general, both symptoms (dyspnea) and respiratory behavior (increased respiratory frequency) can be conditioned to an odorant exposure after a relatively small number of acquisition trials. Although pretrial, unconditioned odor responses appear to have little role in the above outcomes, negative-valency odors are much more efficient conditioned stimuli than positive-valency odors (51–53).

To summarize the evidence pertaining to odor-triggered anxiety states:

- Clinical observations of individuals involved in traumatic (irritant) respiratory tract over-exposures suggest that the same exposure agent, at lower (odorant) concentrations, may subsequently trigger symptoms of anxiety and hyperventilation.
- Similar symptom patterns can be observed among individuals working with CNS toxicants (e.g., solvents with acute, reversible narcotic effects), including a clinical presentation indistinguishable from classic panic disorder.
- Conditioning experiments with human volunteers suggest that odors, particularly from compounds with intrinsic irritancy, can acquire a signal value when presented with an unconditioned stimulus for hyperventilation, and that both symptoms and altered respiratory behavior can subsequently be elicited by the test odorant alone.
- There is some clinical/experimental evidence that the episodic symptom complex of MCS/IEI may involve hyperventilation and/or panic and may occur on an odor-triggered basis.



**Figure 7.** Differential diagnosis of episodic, exposure-triggered dyspnea in the workplace.

## Summary

Air pollutants, including compounds with predominantly odorant qualities, may trigger symptoms locally in (and reflexively from) the upper respiratory tract. Symptoms may be as straightforward as mucous membrane irritation, or as nebulous as mental status changes. A frequent component of unexplained symptom complexes is the complaint of dyspnea, or shortness of breath. As noted in Figure 7, three conditions—asthma, VCD, and panic attacks—have as an essential feature the complaint of episodic dyspnea. Careful history-taking, including a description of the dyspnea (“do you have trouble getting air in or out?”), associated glottic symptoms (globus, hoarseness, stridor), and associated autonomic/CNS symptoms (paresthesias, palpitations, sweating, chest pain, gastrointestinal distress, sensation of depersonalization/derealization, sense of impending doom) may assist in this sometimes difficult differential diagnosis (54). Other poorly understood symptom complexes involving the upper airway, including nonallergic rhinitis and irritant-induced rhinitis, remain to be elucidated in terms of both mechanism and strict case definition.

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