The Vomeronasal Organ and Chemical Sensitivity: A Hypothesis

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Environmental exposures to very low levels of airborne chemicals are associated with adverse symptoms, often affecting multiple organ systems, in the phenomenon of chemical sensitivity (CS). Recent surveys suggest a significant prevalence of chemically sensitive subjects in the United States, but the mechanism linking exposure to symptoms remains unclear, despite the advancement of a variety of theoretical models. In many of these models, exposure of the nasal respiratory system to an airborne agent is the first step in the pathway leading to symptoms. In this article, we advance the hypothesis that interactions between environmental chemicals and the vomeronasal organ (VNO) may play a role in the etiology of CS. The VNO, a bilateral, tubular organ located in the nose, serves in animals as part of a sensitive chemosensory system; however, evidence suggesting that the VNO retains a functional role in the adult human is controversial. Reported characteristics of the human VNO relevant to CS, including location, prevalence, selective sensitivity to airborne chemical exposure, and capacity to produce systemic effects, are discussed within the context of this ongoing debate. Beyond relevance to CS, the demonstration of an active, adult VNO could have significant impact on environmental toxicology. ***Key words:*** **chemical intolerance, chemical sensitivity, environmental intolerance, MCS, multiple chemical sensitivities, VNO, vomeronasal organ.** ***Environ Health Perspect*** **110(suppl 4):655–661 (2002).**
http://ehpnet1.niehs.nih.gov/docs/2002/suppl-4/655-661greene/abstract.html

Environmental exposures to low levels of airborne chemicals have been associated with adverse symptoms in susceptible persons, even though such exposures are tolerated by the majority of the population without adverse reaction (*1*). A wide variety of controversial labels have been applied to the conditions of such chemically sensitive patients, including multiple chemical sensitivities (MCS), environmental illness, idiopathic environmental intolerance, chemical hypersensitivity syndrome, chemical intolerance, twentieth century disease, and odor intolerance, among others (*2–4*). Contemporary conditions that may overlap with or include components of chemical sensitivity (CS) include sick building syndrome, fibromyalgia, chronic fatigue syndrome, and Gulf War illness (*5–8*).

Symptoms reported by chemically sensitive patients upon exposure typically involve multiple organ systems and may include headache, fatigue, difficulty concentrating, depression, dyspnea, cough, nasal congestion, muscle and joint pain, nausea, dizziness, abdominal pain, and paresthesias. In view of the diffuse symptom constellation and the lack of an accepted, identifiable mechanism linking symptom to exposure, the nature (and even existence) of these conditions has been the subject of much controversy within scientific (*2,9–13*), regulatory (*12,14,15*), social (*16,17*), and judicial (*18*) arenas. Whether or not these symptoms ultimately have somatic or psychosomatic etiology, the experience and consequences for the affected individuals are very real. Among these chemically sensitive individuals, alterations in lifestyle may result from self-treatment through active avoidance of perceived triggering chemicals; in some cases, significant disability may follow (*15,19–23*).

Nomenclature and definitions are difficult when individual responses to environmental chemical stimuli fall short of easily recognizable disease end points (*24,25*), and a plethora of definitions relating to different facets of the phenomenon of CS have appeared in the literature (*4,19–21,25–30*). Here we will use the general term "chemical sensitivity" (CS) to describe individuals who report the development of symptoms upon exposure to various airborne stimuli but who may or may not perceive themselves to be chronically ill as a result of those symptoms and may or may not have sought health care for their alleviation. The term "multiple chemical sensitivities" (MCS) will refer to individuals who perceive themselves as ill and meet the criteria originally proposed by Cullen in 1987 (*26*). Thus, CS will include the entire spectrum of the phenomenon, ranging from odor intolerance and cacosmia to building-related illness and MCS.

Although considerable attention and debate have focused in recent years on the MCS subset (*21,24*), the general phenomenon of CS may be viewed in a broader context. Thus, the excess of adverse symptoms reported among communities located near toxic waste sites or sources of air pollution, or after chemical spills or accidental industrial chemical releases (*10,31*), as well as health complaints from workers in buildings [e.g., U.S. Environmental Protection Agency employees exposed to outgassing from new carpet (*32*)], from groups claiming sensitivity to particular gasoline additives [e.g., methyl *tert*-butyl ether (*33*)], from communities exposed to pesticide spraying (*34*) or wood preservatives (*35*), or from veterans of the Persian Gulf War (*5,6*) may all represent different expressions of a general, but poorly understood, mechanism of toxicity. That specific mechanisms by which low levels of airborne chemicals may physically interact with the body and produce symptoms have not yet been elucidated does not mean such mechanisms are unlikely to be defined but rather that they may not be easily categorized into currently understood pathways of disease and pathology. The common, but by no means universal, finding of psychiatric co-morbidity has led to controversy regarding appropriate diagnostic and therapeutic approaches for these patients (*23,36*).

As with any illness, whether perceived or clinically accepted, the relevance of CS to the public interest depends in part on the prevalence or incidence of the condition. Until recently, the epidemiology of CS was poorly characterized, but studies completed within the last few years suggest that CS, in its various forms, may be much more common than previously recognized. In a survey of 643 undergraduate college students, Bell et al. (*20*) found that 66% reported feeling moderately to markedly ill after exposure to low levels of at least one of five common environmental odors: pesticide, car exhaust, drying paint, new carpet, and perfume. Some 15% reported similar reactions to at least four of these exposures. In a larger prevalence study, Meggs et al. (*37*) reported results from a population-based telephone survey in rural North Carolina: some 33% of 1,027 individuals polled reported CS, comparable to the percentage reporting allergy. Recently, a landmark article by Kreutzer et al. (*38*) described

This article is part of the monograph *Environmental Factors in Medically Unexplained Physical Symptoms and Related Syndromes.*

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This publication was made possible in part by grants K23 ES00385 and P30 ES05022 from the National Institute of Environmental Health Sciences (NIEHS). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIEHS.

Received 3 December 2001; accepted 18 June 2002.

data from a rigorously conducted telephone survey of more than 4,000 Californians. Some 6.3% reported a prior formal diagnosis of MCS or environmental illness by a doctor, and nearly 16% reported being "allergic or unusually sensitive" to everyday chemicals. In addition, the results showed surprising homogeneity across income, employment, and educational levels.

Although case definitions in each study differed (and the Kreutzer study did not include a specific definition), the above results suggest that both self- and physician-diagnosed chemical sensitivity are common phenomena in the United States. Rising public awareness of CS, regardless of etiology or demonstration of causality, may ultimately provide another source of input to the development and implementation of regulatory policy. If low-level chemical exposures are eventually recognized to be causally related to adverse health effects in some sensitive subset of the population, even if manifested only as undesired symptoms, then adjustment of environmental policy and regulatory limits to accommodate those individuals, with potentially enormous economic impact, will need to be considered at a societal level (*15,16*).

Current Theories of Chemical Sensitivity

In chemically sensitive subjects, symptoms are reported at exposure levels well below those associated with known toxicologic mechanisms. The etiology of symptom production in these patients is a subject of continuing controversy and speculation (*1,19,39*), and no consensus has yet been reached. A variety of different models and theories have been proposed to account for various facets of the phenomenon of CS; representative examples are briefly highlighted here.

The olfactory-limbic kindling model invokes the concept of "subconvulsive chemical kindling" (a form of time-dependent sensitization) in the olfactory bulbs and various regions of the brain to explain development of sensitivity to chemicals seen in some subjects after repeated, low-level environmental exposures (*40*). The theory invokes a two-step process, beginning with initiation, in which repeated, intermittent exposures, or a single, intense exposure of the nose acts to produce some form of alteration of olfactory-limbic neural pathways. Subsequently, in the elucidation phase, exposure of the chemical agent to the nose provokes an amplified neural response, ultimately leading to production of symptoms.

Another model proposes that CS arises from neurogenic inflammation, a process that might begin with an irritant molecule binding to sensory nerve C-fibers (*41*) in the skin and mucous membranes, triggering the release of substance P and other mediators of inflammation that may act locally or systemically to account for the varied patterns of symptom presentation in patients with CS. Both the oropharyngeal mucosa (*42*) and respiratory mucosa (*43*) have been cited as possible initial targets for chemical triggers in variants of this model.

The theory of toxicant-induced loss of tolerance seeks to address CS within a toxicologic framework and also involves two phases: initial exposure to a chemical, causing a loss of tolerance by susceptible individuals, followed by heightened responses (*44*). The concept of "masking" is also invoked, in which chronic exposures to multiple triggering agents in the environment may blunt the symptom response observed in single-challenge laboratory investigations.

Classical conditioning on olfactory stimuli has also been suggested as an explanation for CS (*45–47*). Van den Bergh et al. (*48*) have recently reported acquisition and extinction of somatic symptoms in response to odors using a classical Pavlovian paradigm.

Some studies have found that subjects presenting with CS have an elevated frequency of co-existing Axis I psychiatric diagnoses, such as depression, anxiety, and somatoform disorders (*19*). In one study, there was a greater prevalence of somatization symptoms in MCS patients before the onset of the condition, compared with controls (*49*), suggesting that some form of psychological vulnerability may play a role in susceptibility to the condition.

Case reports in which traumatic overexposure to a toxic gas was subsequently followed by typical symptoms of panic on re-exposure to low levels of that gas were cited by Shusterman (*10*) as examples of behavioral sensitization to irritants or odorants. Similar symptoms on exposure to solvent vapors have also been described in workers who did not have identifiable prior traumatic overexposures, and the general phenomenon has been termed "odor-induced panic attack" (*50*).

The diversity of these models and the overall scarcity of experimental data with which to assess their validity highlight the need to broaden the search for readily testable mechanisms of action that may underlie the phenomenon of CS, as well as the need for objective clinical studies. Interactions in the nasal airway are an integral part of several of the above theories of CS. However, a role for the nose and the specific mechanisms that might be involved in the pathogenesis of CS have not yet been experimentally demonstrated. It is the purpose of this article to propose another potential mechanism involving the nasal airway that might be involved in the etiology of CS, namely, interactions between environmental chemicals and the vomeronasal organ (VNO).

The Vomeronasal Organ

The VNO, also referred to as Jacobson's organ, is a bilateral, tubular structure that is located in the nose and has been well studied in a variety of animal species, with apparent sensory functions permitting various forms of chemical communication that may elicit innate reproductive and social behaviors as well as neuroendocrine changes (*51*). The organ is thought to be the site of reception involved in signaling between animals via naturally secreted, putative airborne pheromones (*52,53*). Indeed, a gene family encoding likely pheromone receptors in the rat VNO has been identified (*54*). First reported in an adult human by Ruysch (*55*) in 1703, further description of this organ in animals was presented by Jacobson (*56*) in 1811, and in adult humans by Potiquet (*57*) in 1891. Although the VNO is clearly present in the human fetus, publications during the early part of the 20th century suggested that the organ was atrophic or vestigial in adults (*58*); contemporary textbooks of human anatomy still generally omit a description of the VNO. During the last 15 years, however, a significant and largely unrecognized body of literature has emerged, some of which suggests that this organ may be present in adult humans and that it may retain an active, functional role, at least in some individuals. Comprehensive reviews of the work supporting these concepts have been published by Monti-Bloch et al. (*59,60*).

Nevertheless, the notion of a present and functional VNO in humans remains controversial, and some polarization of the scientific literature is apparent. A recent review devoted a single paragraph to the human VNO and concluded that "the overwhelming evidence would therefore not support a human VNO that is functional in any meaningful way" (*61*). The comments in that paragraph, however, did not appear to have addressed the content of papers cited in the same review that arrived at different conclusions. To our knowledge, the primary published evidence pointing to a functional human VNO has never been directly refuted in a published, experimental study. It is possible that some elements of this ongoing controversy lie outside the bounds of simple, rational, scientific assessment. Below, we briefly summarize the results of some important prior studies addressing the structure, prevalence, activity, and function of the VNO in adult humans.

Structure of the VNO

In the adult human, the VNO has been described as a pair of blind-ended tubes or ducts, typically 2–10 mm long, one per nostril, oriented in an anterior–posterior direction and located under the respiratory mucosa lining each side of the nasal septum (*62*). The VNO opens into the nasal cavity

through a round or oval depression or "pit" in the mucosa, which is typically 0.2–2 mm in largest diameter. The VNO pit has been described as being found in the anterior, inferior region of the septum, several millimeters above the floor of the nasal cavity and some 1–3 cm posterior to the posterior margin of the external naris, near the junction of the septal cartilage and bony septum (*58,59*).

Most prior studies of gross morphology of the human VNO have used cadavers or tissue excised during surgery. However, several recent studies have used modern imaging techniques, for the first time, to study the structure of the VNO in living humans. Trotier et al. (*63*) instilled a contrast agent into seven VNO pits and used helical computed tomography to image the associated ducts. Lengths of the ducts were found to range from 2 to 5.7 mm.

In a study by Abolmaali et al. (*64*), the VNO ducts of 15 subjects with pit diameters of at least 1 mm were infused with a contrast agent, and the ducts were visualized with magnetic resonance imaging. The median duct length was 7 mm, although the shapes and sizes exhibited significant variation (range of lengths, 3–47 mm). The VNO opening was located at a mean distance of about 25 mm from the columella and 9 mm above the floor of the nasal cavity. Of note, the duct was found to cross to the contralateral side of the septum in one case.

The unique ultrastructure of the human VNO has also been described by several authors (*58,62,65*). The tubular organ is lined with a pseudostratified, columnar epithelium that includes at least three morphologically distinct cell types (*62*). One unusual cell type found on the medial wall of the human VNO, the "light cell" (*62*) or "microvillar cell" (*65*), has an apical surface with short microvillar projections and a basal surface that narrows to a thin, axonlike process reaching the basement membrane. Recent experiments, including isolated, whole-cell recordings, have suggested that these cells may be electrically active neurosensory cells with apical receptors activated by binding of naturally occurring pheromones or synthetic analogs [termed "vomeropherins" by Monti-Bloch and colleagues (*59,66*)]. In one study, these cells were found to stain with immunocytochemical neuronal markers (*67*). In other studies, however, antibodies against olfactory marker protein, found in neuronal cells associated with the VNO in some animals, did not stain human VNO epithelial cells (*63*).

In rodents, tracer studies have demonstrated that the VNO forms one part of a complete neurosensory system, which includes receptor cells that communicate with a nerve that follows the olfactory tracts through the cribiform plate and projects to the glomerular layer of the accessory olfactory bulb (*68*). In humans, however, a complete neural connection from the VNO to the brain has not been morphologically demonstrated, and this remains a significant criticism of the hypothesis of a functional human VNO. In addition, the accessory olfactory bulb, although present in the human fetus, is not thought to be present in the adult human brain. However, numerous, small, unmyelinated nerve fibers have been reported in the lamina propria surrounding the human VNO, and it has been hypothesized that these fibers may participate in communicating signals from the VNO to the central nervous system (CNS) (*59*). Several functional lines of evidence, discussed below, suggest that such a connection should not be ruled out and that excitation of the VNO by airborne chemicals may cause neurally mediated changes in physiology and behavior.

Prevalence of the VNO

A number of studies have examined the prevalence of the VNO in adult humans, as identified by observation of the nasal opening of the organ (the VNO pit). An early study by Johnson et al. (*58*) found at least one VNO pit in 39% of 100 adults; examinations were conducted with the naked eye, without magnification. Moran et al. (*62*) described a study of 200 adults with examinations conducted using a 40× binocular operating microscope. Bilateral VNO pits were observed in all 200 subjects, and the authors remarked that a number of the pits would not have been visible without magnification. Stensaas et al. (*65*) reported that VNO pits were identified in 93% of 410 consecutive patients examined for potential nasal plastic surgery and that those in whom pits were not found had structural abnormalities of the nasal septum. In a large study, Garcia-Velasco and Mondragon (*69*) examined 1,000 adult candidates for rhinoplasty and identified VNO pits in 91% (in 102 patients, the pits were not observed until after surgical correction of septal deviation). The prevalence of the pits was about equal in males and females. These data suggest that the VNO pit is present in most adult humans and that examination under magnification is important for identification of smaller pits (*70*).

However, two new studies have reported lower prevalence of the VNO. Trotier et al. (*63*) performed endoscopic examination of 1,842 patients without nasal septal pathology and, during initial examination, found a VNO pit on at least one side in 26% of subjects. Surprisingly, repeated observations on the same subjects, with time intervals ranging from days to months, revealed considerable variability in the observation of the pits (which were classified as well defined, putative, or not present). Of well-defined pits at first observation, nearly 13% became putative and another 13% were not present at second observation. The cause underlying this significant variation in VNO observations was not clear.

In a recent study by Zbar et al. (*71*), 253 subjects were examined using a nasal speculum without magnification, followed by examination with an endoscope or with a 6× operating microscope if a VNO pit was not initially identified. In this study, a pit was defined as associated with a VNO if it was located within prescribed boundaries: 1–3 mm above the floor of the nasal septum and 1–2 cm posterior to the cutaneous aspect of the columella. Using this definition, the VNO prevalence was only 6%.

Finally, an important and recent anatomical study by Jacob et al. (*72*) calls into question the validity of adult human VNO identification in numerous prior studies, through description and characterization of the location and appearance of another little-known structure, the nasopalatine duct (NPD). In some animals, this structure provides direct connection between the oral and nasal cavities and in some cases is associated with the VNO system. In a study of 221 human subject nostrils, a structure identified as the NPD was identified in 94%; in an associated cadaver study (n = 8), the NPD was found in 100% and was bilateral in all. The authors conclude that "Unusually contradictory anatomical descriptions in the human putative VNO literature may be attributable to inexact descriptions or misidentification of structures" (*72*). If further work verifies that prior studies have indeed confused the VNO and the NPD, then the prevalence of the VNO as well as the balance of evidence supporting, and arguing against a functional role for this organ will need to be reassessed.

Electrical Activity of the VNO

Some of the most intriguing evidence in favor of the VNO as an active sensory system in humans comes from studies of the electrical activity of the VNO epithelium by Monti-Bloch and colleagues (*73,74*), using a miniature, triaxial probe (*75*). In these experiments, the center conductor of the probe was placed in the VNO pit of a subject, in contact with the mucosal surface. The inner, hollow, coaxial sheath was connected to pulsed, gas delivery system and provided discrete puffs of test gases at the VNO opening. The outer, hollow sheath was connected to a suction source and acted to scavenge the gas puff, preventing diffusion of the test compound into the olfactory cleft or the nasopharynx. The negative mucosal electrical potential elicited in response to a gas puff, measured with respect

to the reference potential of the glabella, was termed the "electrovomerogram" (*74*), by analogy with the electro-olfactogram similarly obtained at the olfactory mucosa (*76*). Patients tolerated the procedure well and reported no olfactory sensations during the gas puffs.

In experiments reported by Monti-Bloch and Grosser (*74*), on adult subjects, gas puffs containing 15–25 pg of putative human pheromones were applied to the VNO, in a humidified air stream, using pulses of 0.1–1.0 sec in duration; control puffs contained olfactory test stimuli, such as clove oil, or diluent alone. In response to pheromone puffs, typical depolarizations of 4 mV were observed, which subsequently decayed over a time course of several seconds (*73*). Much smaller depolarizations resulted from puffs with diluent alone or with olfactory stimulants. In contrast, when the probe was located on the olfactory mucosa, the olfactory stimulants produced large depolarizations, whereas the putative pheromones produced much weaker responses. Further experiments demonstrated a sigmoidal dose–response curve and compound-specific adaptation.

The mucosal electrical potential response was shown to be specific to the VNO pit, and not a general characteristic of the nasal respiratory mucosa, through a series of experiments in which the probe was sequentially moved along the mucosa, away from the VNO pit, with diminishing response to test puffs (*73*). These results suggest that the VNO mucosa generates a receptor potential in response to stimulation with extremely small amounts of specific chemicals, and that the olfactory and VNO sensory mucosa have different chemical specificities. Although not demonstrating the transmission of this sensory receptor potential to the CNS, or even beyond the local region of the VNO, these data are consistent with the concept of an active VNO sensory epithelium in adult humans. Gender-specific responses were also observed with different putative pheromones (*73,74*). In assessing this work, however, it should be noted that experimental studies confirming (or refuting) the sensitivity and specificity of the VNO mucosal potential response to test exposures have not been published by any other group.

Evidence for a Functional VNO–CNS Connection

Double-blinded, placebo-controlled, randomized trials reported by Berliner et al. (*77*) have presented initial (although nonanatomical) evidence for a functional neural pathway connecting the VNO with pituitary and hypothalamic regions of the brain. In particular, subjects were exposed nasally to 1-sec pulses of a particular synthetic steroidal compound (pregna-4,20-diene-3,6-dione, or PDD), or to a control substance, every 10 min during a 6-hr period. The total amount of PDD delivered to a subject during the course of the experiment was about 10 ng. Statistically significant decrements in measures of luteinizing hormone (LH) pulsatility and LH plasma levels and of follicle-stimulating hormone pulsatility were observed ($p < 0.05$), but only in males exposed to PDD. In addition, significant changes (with short latencies) were observed, after the individual puffs of PDD, in measures of autonomic function including heart rate, respiratory rate, skin conductance, and indices of brainwave activity. Additional control experiments included application of the gas puff to the nasal respiratory and olfactory mucosa and revealed no significant changes in hormone levels or autonomic function. The authors concluded that these data support the concept of an active VNO–hypothalamic–pituitary neural axis (although without any known anatomical correlates), and they pointed out a variety of potential therapeutic uses for VNO stimulants that might affect hypothalamic function, ranging from treatment of anxiety and other CNS disorders to hormone replacement therapy (*78*). In a different study that is consistent with this idea, although not specific to the VNO, Stern and McClintock (*79*), following earlier work by Cutler, Preti, and colleagues (*80,81*), showed that consciously undetected compounds (purported pheromones), when applied to the upper lip and presumably inhaled nasally, altered reproductive cycles in women.

Recent studies by Sobel et al. (*82*) used functional magnetic resonance imaging to examine localized brain activity in response to nasal exposure to a particular airborne vomeropherin (estratetraenyl acetate) that had been shown in earlier studies (*73*) to selectively activate the VNO but not the olfactory system. Significant brain activation was observed, relative to control exposures, primarily in the anterior medial thalamus and inferior frontal gyrus, and there was evidence for increasing activation with higher concentration of the administered compound. At low vomeropherin concentration, none of the subjects were able to specifically detect the compound consciously, or through forced-choice paradigms, despite significant brain activation. In another experiment using the same test compound, local exposure of the VNO resulted in cortical evoked potentials in the temporal regions, with latencies that could be consistent with involvement of a polysynaptic neural pathway (*59*).

At a higher organizational level, changes in human behavior and cognition arising from exposure to purported VNO stimulants, without olfactory recognition, have recently been reported by Grosser et al. (*83*). In this double-blinded, randomized study of 40 women, a vomeropherin (androstadienone) in a diluent (propylene glycol), or a control (the diluent alone), was locally applied to the VNO for 1 sec in a vapor stream using a miniature, coaxial probe. This probe was apparently the same as that used in earlier studies of VNO mucosal potentials (*74*), and it also included a scavenging system intended to prevent airborne diffusion of the applied compounds beyond the local area of the VNO pit. A modified version of a validated neuropsychological questionnaire was filled out before the start of each session and 45 min after exposure. A variety of autonomic indicators [respiratory and cardiac rates, galvanic skin response, body temperature, electroencephalogram (EEG)] were also monitored before and after the exposure. Statistically significant reductions ($p < 0.001$) in indices of overall negativity, negative affect, and negative character were reported for the experimental group. At 35 min postexposure, significant changes in autonomic measures were noted, including decrements in respiratory and cardiac rates and galvanic skin response, and an increase in alpha-wave component of the EEG; these differences became insignificant at 75 min postexposure.

The study by Grosser et al. (*83*) provided significant evidence that nasal exposure to androstadienone, in a region localized around the VNO opening, resulted in changes of affect and of autonomic indices. The authors concluded that activation of the VNO represented the first step in the mechanism of action of androstadienone. Although the evidence presented is consistent with this idea, a stronger conclusion would have been reached if another control experiment had been performed in which regions of nasal mucosa other than that near the VNO were exposed to the pulse of androstadienone. Note also that objective data demonstrating the efficacy of the vapor scavenging system has not been published, and incomplete scavenging would raise the possibility that other mechanisms, such as direct absorption into the bloodstream through the nasal mucosa, or periaxonal transport along olfactory neurons into the brain, could have contributed to the observed results.

Potential Relation of the VNO to Chemical Sensitivity

As a whole, the body of work cited above suggests that nasal exposures to low levels of certain natural or synthetic airborne chemicals may alter CNS activity and function, with resultant changes in behavior and physiology, even in the absence of direct, conscious awareness of the exposure. Limited but intriguing evidence supports activation of the

VNO as the first step in that process. If such a sensory–cognitive–physiologic pathway exists, mediated by the VNO, it would represent a candidate mechanism for the phenomenon of CS. Extremely low levels of putative pheromones or synthetic vomeropherins have been shown, in isolated studies, to affect both the peripheral and central nervous systems; similarly, exposure to very low levels of airborne chemicals are thought to produce symptoms in chemically sensitive subjects. The changes in autonomic function and behavior that have been reported to result from VNO exposure to vomeropherins (*59,84*) are consistent with a potential role in CS. If exposure of the VNO to certain compounds (e.g., androstadienone) results in positive changes in affect, it is not unreasonable to hypothesize that exposure to other compounds might result in negative changes via a similar pathway, contributing to expression of the phenomenon of CS.

Differential sensitivity or prevalence of the VNO among the population might then play a role in determining susceptibility to manifesting CS. As a corollary, subpopulations exhibiting dominantly positive changes in affect and measures of well-being on exposure to environmental chemicals might also exist, but such individuals would be unlikely to come to the attention of the health care system as a result of such sensitivity. The true prevalence of the VNO in adult humans is clearly unknown, although recent estimates of 6–25% are similar to a recent estimate of the prevalence of CS (16%). The suggestion by Jacob et al. (*72*) that confusion between the VNO and the NPD could be widespread in the existing literature may require a critical reexamination of much prior work in this area and highlights the need for further well-controlled experiments, but it does not diminish the possibility that patterns of differential expression of the VNO may be identified.

Among many possible mechanisms, one way in which the multi-organ system nature of typical symptoms reported by chemically sensitive subjects might arise is from alterations in systemic hormone levels elicited by VNO-mediated neuroendocrine activation. As discussed above, prior studies have presented evidence linking VNO activation with altered levels or temporal release patterns of certain systemic hormones (*77,84*). It is conceivable that other hormone levels or patterns of release might be affected in an analogous fashion.

In numerous studies, acute and chronic changes in hormone levels have been associated with a broad range of symptoms, including many that are reported in subjects with CS. Potential CNS effects are legion (*85*), and endocrine abnormalities are frequently associated with disorders in behavior, mood, and cognitive function (*86*). As examples, chronic fatigue, anxiety, and emotional lability may be early symptoms arising from hyperthyroidism. Transient hypomania may be associated with the onset of thyroid hormone replacement therapy in hypothyroid patients. Anxiety and irritability are seen in up to a third of patients with hyperparathyroidism, and fatigue, weakness, and depression are also common. Alterations in sensory thresholds to olfactory stimuli have been reported in the hypoadrenal Addison's patient; acute mania may result when such a patient is started on replacement corticosteroids. Withdrawal of progesterone is thought to precipitate depression in some women.

Many patients with CS complain of respiratory symptoms; others complain of muscle pain or nonspecific gastrointestinal symptoms. Changes in hormones mediated by the hypothalamus could play a role in the etiology of these symptoms as well. For example, corticotropin-releasing hormone and progesterone are both respiratory stimulants, whereas cyclic decreases in progesterone have been associated with premenstrual exacerbations of asthma (*87*). The onset of hyperthyroidism has been linked to increased bronchial reactivity, and such patients may also present with chronic or acute abdominal pain that resolves on hormone replacement. Hypothyroidism can be associated with spontaneous muscle cramps (of neural origin) and muscle aches (from abnormal contraction and relaxation) (*88*). Nonspecific abdominal pain is also found in about a third of patients with adrenal insufficiency (*89*).

Thus, we speculate that changes in levels or temporal release patterns of a combination of systemic hormones, mediated by VNO-stimulated neuroendocrine changes, could potentially account for, or contribute to, the diffuse symptomatology seen in subjects with CS. To our knowledge, no systematic, controlled study of hormone levels or temporal release patterns in such subjects has yet been published.

Experimental Testing of the Hypothesis

The hypothesis that a relationship exists between the phenomenon of CS and the VNO is amenable to experimental investigation. At the broadest level, previous anatomical studies suggest that only a fraction of the population has an identifiable, patent, VNO duct. If the VNO is, in fact, a necessary part of the pathway leading to CS, then the frequency of identification of a patent VNO duct would be expected to be considerably higher in those with the condition than in nonsensitive control subjects. Similarly, the size of the VNO opening into the nasal cavity may regulate exposure of the purported neurosensory cells lining the VNO by controlling diffusion of airborne chemicals into the duct. If so, an association could be expected between mean area (or other geometric index) of the duct opening and the presence or severity of CS. Standard statistical techniques can be used to assess the strength of such associations. Our laboratory has recently begun a study of VNO prevalence and morphology in chemically sensitive and control subjects, with a goal of determining whether differential expression and/or structure of the VNO are correlated with the diagnostic label of CS (*90*).

We plan further experimental tests, with potential applications to treatment, that include modification of exposure of the VNO in subjects with a diagnosis of CS. This experimental approach uses a pool of subjects with CS and an identifiable airborne exposure previously determined to result in adverse symptoms. In a clinical trial involving controlled exposures to the specific airborne agents, assessment of differences in symptom reporting, with and without functional or physical blocking of the VNO duct opening, may provide evidence for or against involvement of the VNO in the mechanism of CS.

Finally, our speculation concerning the potential role of hormones in the mechanism of CS can also be subjected to experimental test. Specifically, the level and temporal release patterns of candidate hormones could be examined through blood assays in chemically sensitive and normal subjects before and after test exposures of the VNO to airborne agents. Statistically significant differences among the groups in measures of pattern of hormone release, such as peak levels, time-integrated levels, or latencies, would support potential involvement of systemic hormones in the etiology of CS. Although associations alone do not demonstrate causality, a positive result from such a study would provide significant impetus to focus attention on this pathway.

Summary

The phenomenon of sensitivity to low levels of airborne, environmental chemicals is increasingly recognized as a cause of morbidity and economic loss in the United States, with recent estimates suggesting that tens of millions of people may be affected. The etiology of symptom production in these subjects is not understood and is the subject of considerable controversy. A number of diverse mechanisms and models have been proposed to explain the symptoms associated with CS, and initial interactions in the nasal respiratory system are integral to many of these. To date, there is no widely accepted mechanism of action, and controlled studies designed to evaluate the various theories have been scarce and have yielded inconsistent results.

The interaction of airborne chemicals with the VNO represents an intriguing candidate mechanism of toxicity in CS that has been entirely unexplored. Although evidence supporting functionality of the human VNO is controversial, reported characteristics of the VNO are relevant to the phenomenon of CS. For example, although estimates of the prevalence of the VNO vary widely, figures from recent publications are similar to a recent estimate of the prevalence of CS. We speculate that differential expression or sensitivity of the VNO could play a role in determining susceptibility to CS. In certain experiments, the VNO has responded (at least locally) to extremely small quantities of particular airborne chemicals, consistent with the very low levels of exposure that trigger symptoms in subjects with CS. Controlled human trials have provided evidence that excitation of the VNO may affect CNS-mediated functions, observed as changes in indices of affect and in patterns of hormone production. Among many potential mechanisms, we hypothesize that altered hormone release patterns could contribute to the diffuse symptomatology seen in subjects with CS.

Discovery that the VNO is integrally involved in a pathway leading to CS could foster the design of appropriate therapy to reduce activation or exposure of this organ. Because no therapy or intervention has thus far been shown in controlled trials to be effective for chemically sensitive patients, the demonstration of a therapeutic option would be of considerable importance to this group.

The potential significance of an active VNO extends far beyond work with the chemically sensitive population. Should the limited evidence discussed above be confirmed, then interaction of the VNO with trace amounts of environmental airborne chemicals may have a broad spectrum of potential clinical consequences. Our intent here is to bring the VNO, although little known and controversial, to the attention of the environmental health community. Demonstration of an active, adult VNO could be of great significance if linked to the phenomenon of CS but would also potentially open a new field of environmental toxicology.

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