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INVITED MEDICAL REVIEW

Olfaction in dentistry

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Practitioners of oral medicine frequently encounter patients with complaints of taste disturbance. While some such complaints represent pathological processes specific to the gustatory system, *per se*, this is rarely the case. Unless taste-bud mediated qualities such as sweet, sour, bitter, salty, umami, chalky, or metallic are involved, 'taste' dysfunction inevitably reflects damage to the sense of smell. Such 'taste' sensations as chicken, chocolate, coffee, raspberry, steak sauce, pizza, and hamburger are dependent upon stimulation of the olfactory receptors via the nasopharynx during deglutition. In this paper, we briefly review the anatomy, physiology, and pathophysiology of the olfactory system, along with means for clinically assessing its function. The prevalence, etiology, and nature of olfactory disorders commonly encountered in the dental clinic are addressed, along with approaches to therapy and patient management.
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Introduction

The nose and mouth are sentinels of our chemical world. They allow us to experience life chemically, thereby guiding us, protecting us, feeding us, and helping us to breathe. In fact, all environmental nutrients and airborne chemicals necessary for life enter the body via the nose and mouth. Olfaction, along with its sister sense of taste, monitors the intake of such materials and largely determines the flavor and palatability of foods and beverages. This sensory system warns of such dangers as spoiled food, leaking natural gas, polluted air, and smoke, and in dysfunction can be an early indicator of such serious diseases as Alzheimer's disease and Parkinson's disease (Hawkes and Doty, 2009). Chemosensory disturbances significantly impact quality of life and can alter food choices, ingestion, body weight, nutrition, and perhaps even immunity. Such compromise can result in malnutrition and worsening of medical illnesses. For example, increased use of sugar and salt to compensate for diminished chemosensation can be detrimental to those with diabetes mellitus or hypertension (Bromley, 2000).

In addition to consequences on well-being, loss of smell function can lead to economic hardship. Thus, a good sense of smell is critical for those in many occupations, including cooks, wine merchants, plumbers, policemen, firemen, perfumers, and employees of numerous chemical, gas, and public works industries. Attesting to its importance in the military is the fact that anosmia (loss of smell function) is a cause for dismissal from the United States Armed Forces, including the Coast Guard. Indeed, screening for smell dysfunction is an element of the initial physical examination of recruits to these services.

In this review, we summarize key aspects of the anatomy and physiology of the olfactory system, clinical syndromes in which is it compromised, and up-to-date techniques for quantitatively assessing its function. Such assessment is critical for (a) establishing the validity of a patient's complaint, (b) characterizing the specific nature of the chemosensory dysfunction, (c) directing patients to appropriate care by a specialist, (d) accurately monitoring medical and surgical interventions, (e) detecting malingering, and (f) establishing appropriate disability compensation.

Anatomy and physiology

Smell

During inhalation, an estimated 10–15% of the air entering the nose reaches the region of the ciliated olfactory receptor cells, whose dendrites, cell bodies, and axons are embedded within a pseudostratified columnar epithelium lining the upper recesses of the nasal cavity. Alterations in naso-sinus structure and nasal airway patency can have a significant influence on the ability of odorant molecules to reach olfactory receptors (Keyhani *et al*, 1995). The act of sniffing modulates this incoming

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airflow, and sniffing alone can independently activate and 'prime' brain regions associated with odor perception, including the piriform cortex, orbitofrontal cortex, and cerebellum (Sobel *et al*, 1998).

After being inhaled, odorant molecules absorb into the olfactory mucus and reach the cilia via diffusion or transport by specialized 'carrier' proteins (Pelosi, 1994). The 6–10 million olfactory receptor cells are located within an epithelial matrix of supporting cells, other cell types, and ducts from specialized mucus secreting glands, termed Bowman's glands (Menco, 1997). The ~450 functional receptor types to which odorants bind are located on the membranes of the 10–30 thread-like cilia which extend into the mucus from the dendritic knob of each receptor cell. However, each receptor cell expresses only one type of olfactory receptor protein to which odorant molecules reversibly bind (Mombaerts, 2001).

Most olfactory receptor proteins are activated by multiple chemicals, resulting in overlap between the responsiveness of the receptor cells to the same chemical. The diversity of receptors greatly exceeds that of any other sensory system. In vision, for example, only four different types of receptors are found – three types of cones and one type of rod. A picture of the olfactory epithelium and some ciliated receptor cells is shown in Figure 1.

The olfactory receptor cells are unique in a number of ways (Menco and Morrison, 2003). First, their cilia lack the dynein arms responsible for the motility of other cilia, so they do not beat in unison, more or less wafting in the mucus. Second, they serve as both the receptor cell and the first-order neuron. Third, when damaged, they can be replaced by stem cells located deep in the epithelium, although such replacement is rarely perfect and, in some cases, other cell types replace regions previously occupied by the receptor cells. Fourth, they can transport a number of exogenous agents, including viruses, bacteria, and toxins, from the nasal cavity directly into the brain. Indeed, it was found in the first half of the 20th century that the polio virus commonly entered the brain via this route, leading to public health initiatives in Canada and elsewhere to cauterize the olfactory region of school children chemically in attempts to prevent the contraction of polio (Doty, 2008).

Figure 1 A transition region between the human olfactory (bottom half) and respiratory (top half) epithelia. Arrows signify two examples of olfactory receptor cell dendritic endings with cilia. From Menco and Morrison, 2003, with permission. © 2003 Marcel Dekker, Inc

The axons of the olfactory receptor cells enter into the olfactory bulb after having passed through the cribriform plate in discrete bundles, termed fila. Within the bulb, they synapse with dendrites of second-order neurons within the glomeruli, globe-like structures which make up a distinct layer of the olfactory bulb. In young persons, thousands of glomeruli are present, whereas in older persons they often are absent, losing their integrity as a result of damage to the incoming olfactory receptor cells (Smith, 1942; Meisami *et al*, 1998). Numerous feed-back and feed-forward circuits are present in the olfactory bulb, resulting in significant modulation of the information coming from the receptors before it passes via the second-order neurons, termed mitral and tufted cells, to the olfactory cortex.

It is noteworthy that each glomerulus receives input from receptor cells that express the same type of receptor. Moreover, the type of receptor protein dictates the glomerulus to which the cell projects (Mombaerts *et al*, 1996). Thus, in mice in which one olfactory receptor protein has been genetically substituted for another, the cell targets the glomerulus associated with the substituted receptor, not the original receptor. Interestingly, as in the olfactory epithelium, regeneration can occur within the bulb. Thus, some cells, including cells that modulate activity among glomeruli (e.g., periglomerular cells) and other cells that alter the activity of the second-order neurons (e.g., granule cells), are replaced by the activity of stem cells. Primordial cells germinate within the subventricular region and migrate peripherally to the olfactory bulb along a path known as the rostral migratory stream, ultimately differentiating into granule and periglomerular cells (Kirschenbaum *et al*, 1999; Bedard and Parent, 2004).

Cortical regions that receive olfactory bulb output include the anterior olfactory nucleus, the pyriform cortex, regions of the amygdala and periamygdaloid complex, and the rostral entorhinal cortex (Price, 1990). This pattern of largely ipsilateral and direct cortical connections that occur without first synapsing in the thalamus likely explains, in part, the strong associations between odors and memory, emotion, and endocrine function. Major elements of the olfactory cortex, such as the pyriform and entorhinal cortices, are critical for

odor identification and ultimately odor perception. For example, the pyriform cortex is active in tasks involving long-term odor recognition and the determination of odor familiarity. Nonetheless, lesions within the primary olfactory cortex, such as those inflicted by ablating the amygdala and hippocampus for control of intractable epilepsy, influence a range of olfactory measures, including those of odor identification, detection threshold sensitivity, and odor discrimination (Hawkes and Doty, 2009).

Taste

Although not the focus of this review, it is important for the oral health professional to keep in mind that some complaints of 'taste dysfunction' actually involve the taste system proper. This system, which works in concert with olfaction in determining the flavors of foods and beverages, is more resilient to injury than the olfactory system. This is in large part because of the fact that multiple nerves are responsible for transmitting taste information to the brain, including the chorda tympani branch of the intermediate nerve (generally considered part of the facial nerve CN VII), the glossopharyngeal nerve (CN IX), and the vagus nerve (CN X) (Figure 2). These nerves supply gustatory information from the overlapping regions of the orophayngeal cavity, and, as such, help to protect an individual from a generalized loss of taste (ageusia) as a result of an isolated peripheral nerve injury (Witt *et al*, 2003). While the taste buds exist in the papillae of the tongue and the epithelium of the palate, there are now recognized extralingual locations, including the oropharynx, larynx, and the upper esophagus. Although it is not clear if extralingual taste buds are functionally different from the lingual buds, the buds on the epiglottis and uvula may be involved in the initiation of upper airway reflexes and potentially salivary gland modulation (Witt *et al*, 2003). It is important to note that the trigeminal system contributes somatosensory elements to the overall flavor experience (e.g., spicy hot, tingling, burning, and cooling).

The mucosa of the nasal and oral cavities needs to remain moist to be healthy. Taste buds are continually bathed in secretions from the salivary glands. Saliva plays an essential role in lubricating the taste buds, facilitating taste transduction, and protecting taste receptors from potentially damaging acids, bases, and many chemical toxins (Bradley and Beidler, 2003). Inadequate salivary flow, as in xerostomia, may ultimately be a means by which many conditions cause taste disturbance.

Tests for measuring olfactory dysfunction

As indicated in Table 1, there are numerous tests described in the literature for clinically assessing a patient's ability to smell. Although some tests require complex stimulus presentation and recording equipment, most do not. Tests routinely used in the clinic rely on the patient's ability to identify odors (identification tests) or to detect low concentrations of odors (threshold tests). In a few cases, tests of the ability to discriminate among odors have been used, although such tests do not add much additional information to a clinical olfactory test battery. Identification tests are the most widely employed, in part because of their ease of administration (in some cases being able to be self-administered), high reliability, proven validity, short administration time, and relatively strong correlations with more time-consuming olfactory tests, including threshold tests. Both forced-choice odor identification and single staircase detection threshold paradigms were pioneered by our center and are described in this section, followed

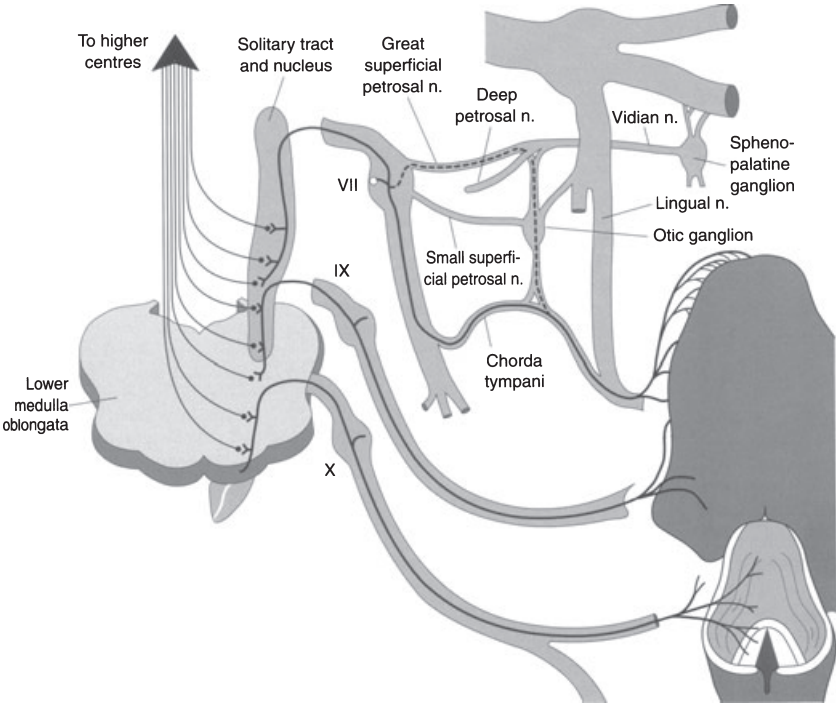

Figure 2 Major taste pathways. Taste buds in the oral cavity are innervated by cranial nerves VII, IX, and X. The first-order nerves terminate in the medulla (nucleus of the solitary tract). The second-order neurons ascend to the parvicellular division of the ventroposteromedial nucleus of the thalamus. The primary taste cortex is located in the anterior insula. Adapted from Netter, 1964. © 2004 Richard L. Doty

Table 1 Clinical psychophysical Olfactory tests. Modified from Doty, 2007

Identification tests	*Threshold tests*
Alberta Smell Test (Green and Iverson, 1998)	Alcohol Sniff Test (Davidson and Murphy, 1997)
Barcelona Smell Test (Cardesin *et al*, 2006)	Amoore Threshold Test (Amoore and Ollman, 1983)
Biolfa Olfactory Test (Bonfils *et al*, 2004)	Biolfa Olfactory Test (Bonfils *et al*, 2004)
Brief Smell Identification Test (B-SIT) (Doty *et al*, 1996)	The Smell Threshold Test (Doty, 2000)
Connecticut Chemosensory Clinical Research Center Test (Cain *et al*, 1983)	Connecticut Chemosensory Clinical Research Center Test (Cain *et al*, 1983)
Combined Olfactory Test (Lam *et al*, 2006)	Combined Olfactory Test (Lam *et al*, 2006)
European Test of Olfactory Capabilities (Thomas-Danguin *et al*, 2003)	Toyota & Takagi (T&T) Olfactometer (Takagi, 1989)
Sniffin Sticks (Kobal *et al*, 1996)	Sniffin Sticks (Kobal *et al*, 1996)
Jet stream Olfactometer (Ikeda *et al*, 1999)	
Kremer Olfactory Test (Kremer *et al*, 1998)	
Le Nez du Vin (McMahon and Scadding, 1996)	
Odor Confusion Matrix (Wright, 1987)	
Odor Stick Identification Test (Saito *et al*, 2006)	
Pocket Smell Test (Duff *et al*, 2002)	
Quick Smell Identification Test (Q-SIT) (Jackman and Doty, 2005)	
San Diego Odor Identification Test (Anderson *et al*, 1992)	
Scandinavian Odor Identification Test (SOIT) (Singh and Dominic, 1981)	
Smell diskettes (Simmen *et al*, 1999)	
University of Pennsylvania Smell Identification Test (UPSIT) (Doty *et al*, 1984)	
Viennese Odor Test (Lehrner and Deecke, 2000)	

by a description of electrophysiological measures currently available for assessing smell function.

University of Pennsylvania Smell Identification Test
This widely used 40-odorant smell test is known in the scientific and medical literature as the University of Pennsylvania Smell Identification Test (UPSIT) and is commercially available as the Smell Identification Test (Sensonics, Inc., Haddon Hts, NJ, USA). This test focuses on the relative ability of individuals to identify odors at the suprathreshold level (Doty *et al*, 1984). Physically, it is comprised of four test booklets with 10 pages each (Figure 3). A microencapsulated 'scratch & sniff' odorized strip is present at the bottom of each page, just below a four-alternative, multiple-choice question. The patient smells an odorant after releasing it from the scratch-and-sniff label and indicates the identity of the odor from the four alternative choices that are provided. An answer column located on the back page of each booklet provides a template for scoring. Based on the test score, which ranges from 0 to 40, one can establish an absolute indication of function (i.e., normosmia, mild microsmia, moderate microsmia, severe microsmia, and total anosmia) and a relative indication of function (percentile rank relative to the patient's age and gender). Malingering can also be detected based on the improbable responses arising from the forced-choice format, i.e., scores below 6. Although the 40-item UPSIT remains the 'gold standard' of olfactory tests, reflecting its ease of use and high reliability (test–retest $r > 0.90$), briefer variants have been developed, including 3- and 12-item versions (Doty *et al*, 1996; Jackman and Doty, 2005). While the latter tests are useful for screening for severe dysfunction, they do not discriminate among categories of dysfunction and are unable to detect malingering.

The Single Staircase Odor Detection Threshold Test
In the late 1970s, we were the first to adopt a staircase procedure for assessing olfactory thresholds (Doty, 1978), a paradigm previously employed in other sensory systems (Doty, 1969). Using a standard algorithm, an odorant's concentration is decreased after trials when correct detection occurs and increased after trials when correct detection does not occur. On a given trial, the subject is asked to indicate which of two stimuli (i.e., an odorant and a blank presented in random order) seems strongest, rather than simply reporting the presence or absence of a smell. This largely avoids the influences of criterion or response biases. An average of four or more up–down transitions ('reversals') is used to estimate the threshold value (Deems and Doty, 1987).

There are a number of practical limitations of olfactory threshold tests, such as the one described above. First, unlike the UPSIT and similar tests, an examiner is needed to administer the test. Second, a relatively large number of trials is required to establish reasonable reliability, resulting in test sessions lasting a half-hour or more. Third, odorants need to be replaced regularly as they become weaker or, in some cases, oxidize or otherwise change their character over time. Fourth, while in most cases lower sensitivity to one chemical reflects lower sensitivity to other chemicals, this is not always the case and instances of 'specific anosmias' or 'specific hyposmias' have been documented. Hence, for most routine clinical purposes, olfactory threshold tests should be administered in conjunction with odor identification tests.

Electrophysiological tests
Two electrophysiological measures have been used clinically for assessing olfactory function. The first, the electro-olfactogram (EOG), is a measure of summated receptor cell generator potentials obtained from the

Figure 3 The four booklets of the University of Pennsylvania Smell Identification Test. Each page of each 10-page booklet contains a microencapsulated odorant that is released by scratching with a pencil tip, along with a multiple-choice question on which of four alternatives smells most like the stimulus. Forced-choice answers are recorded on the last page of the booklet and assessed with a simple scoring key. Photograph courtesy of Sensonics, Inc., Haddon Hts., NJ, USA. Copyright © 2008, Sensonics, Inc

surface of the olfactory epithelium (Ottoson, 1956). However, its clinical usefulness is limited by a number of factors: a significant number of patients are unable to tolerate electrodes placed into their non-anesthetized noses, subtle changes in electrode placement can alter recording fidelity, and EOG responses are present in many anosmic individuals and can be measured even after death. In some diseases with known smell loss, such as schizophrenia, EOG responses are larger, not smaller, than normal. The second, the olfactory event-related potential, has proven to be more useful, as it can assess the magnitude and timing of central neural activity induced by odorants pulsed into the nose (Kobal, 2003). However, its measurement requires complex and expensive stimulus presentation equipment, as well-delineated pulses of odors with rapid rise times must be presented without evoking intranasal somatosensory activity. Expensive recording equipment is also needed, as subtle changes in EEG activity must be filtered from the background of considerable neural noise. Although of potential value in detecting malingering, cooperation on the part of the subject, such as sitting very still during recording sessions, is still needed for their reliable measurement. Additionally, inclusion or exclusion of potentials is visually made by the experimenter, opening up the possibility for bias in the selection of potentials to be included in the analysis.

Types and causes of smell dysfunction

The ability to smell is influenced by a number of factors, including age, gender, nutrition, health, accidents/injury, smoking habits, and reproductive state (Murphy *et al*, 2003). Some are transient, such as the decreased olfactory sensitivity that occurs following eating or the depression in smell function that occurs when the nasal cavity is temporarily inflamed and/or obstructed. Women typically outperform men on tests of odor discrimination, recognition, and detection, and retain normal smell function to a later age than do men (Doty and Cameron, 2009). Smell loss is very common in later life, with significant decrements being present in approximately half of those between 65 and 80 years of age and three-fourths of those 80 years of age and older (Figure 4). Such dysfunction undoubtedly contributes to the disproportionate number of elderly persons who die in accidental natural gas poisonings and explains why many elderly persons report that food has little flavor (Chalke *et al*, 1958; Duffy *et al*, 1995). In some cases, smell loss results in nutritional disturbances and even death. As noted previously, it is underappreciated that most food flavors are dependent upon the stimulation of the olfactory receptors from the rear of the nose during mastication. Taste buds primarily mediate such sensations as sweet, sour, bitter, and salty, as well as those derived from monosodium glutamate and similar salts (umami, chalky, and metallic).

Nearly two-thirds of cases of chronic anosmia or hyposmia (i.e., those that are presumably permanent) are caused by upper respiratory tract infections, head injury, and nasal and paranasal sinus pathology, and most reflect damage to the olfactory neuroepithelium (Deems *et al*, 1991) (Table 2). Other causes include iatrogenic interventions (e.g., turbinectomy, septoplasty, rhinoplasty, and radiotherapy), intranasal neoplasms (papilloma, hemangioma, ameloblastoma, etc.), intracranial space occupying lesions (Foster Kennedy syndrome, olfactory groove meningioma, and frontal lobe glioma), epilepsy, psychiatric disorders, exposure to environmental chemicals, hypothyroidism, and renal or liver disease. Anosmia or hyposmia is a well-recognized primary or sole feature of an olfactory groove meningioma (Finelli and Mair, 1991). Moreover, as mentioned at the beginning of this review, olfactory dysfunction may be an early sign of Alzheimer's disease (Doty *et al*, 1987), idiopathic Parkinson's disease (Doty *et al*, 1988b), and some other associated diseases (e.g., Lewy body disease) (Westervelt *et al*, 2003). In most patients with congenital anosmia, imaging studies reveal a lack of, or marked hypoplasia of, the olfactory bulbs and stalks bilaterally (Yousem *et al*, 1996). Although numerous drugs reportedly influence chemosensation – including some chemotherapeutic agents, antidepressants, antibiotics, antifungals, antihypertensives, and antihyperlipidemics – their influences are primarily on the taste, not the smell, system (Doty and Bromley, 2004).

Most smell distortions, i.e., dysosmias and phantosmias, reflect dynamic elements within the olfactory epithelium associated with degeneration – or more rarely regeneration – and spontaneously resolve over time. In essence, most such phenomena can be likened to other forms of neuronal paresthesia experienced elsewhere in the body that result in selective and variable experiences that depend on the specific sensory nerve involved (i.e., 'foot is asleep', 'face is tingling', 'lights flashing', 'ringing in my ears', etc.). Often anosmic or severely hyposmic patients report a prior phase of dysosmia that was present for days or weeks. In some cases, extremely debilitating chronic dysosmias, which

Table 2 Causes and frequency of occurrence of olfactory dysfunction in 750 patients presenting at the University of Pennsylvania Smell and Taste Center (adopted from Deems *et al*, 1991)

Etiologies	*Frequency (%) of subjective loss amongst total*	*M:F*	*Frequency (%) of verified olfactory dysfunction amongst those complaining of a subjective loss*
Upper respiratory infection/cold	26	1:1.7	76.04
Idiopathic	22	1:1.3	52.69
Head trauma	18	1.2:1	85.60
Nasal and paranasal sinus disease	15	1:1	71.55
Congenital	4	1:1	100
Toxic chemical exposure	2	2.6:1	66.66
Oral infection	0.8	1:2	16.66
Other infection	0.5	1:3	25
Psychiatric	0.5	1:1	25
Pregnancy related	0.4	0:3	33.33
Seizure related	0.4	1:2	100
Sarcoidosis	0.3	0:2	50
Lupus	0.3	0:2	0
Multiple chemical sensitivities	0.3	0:2	0
Brain tumor	0.3	0:2	50
Other	3	1:1.2	9.09
Iatrogenic olfactory dysfunction			
Dental procedure	2	1.1:1	46.66
Medication induced	2	1:2.7	60
Nasal operation	1	1:0.1	87.5
Neurosurgery	0.7	1:1.5	60
Radiation therapy	0.5	1:3	75
Ear operation	0.3	0:2	0
Other operation	0.5	1:1	75

have been present for more than a year, are amenable to surgical intervention, such as ablation of portions of olfactory epithelium (Leopold *et al*, 1991) or removal of olfactory bulbs (Kaufman *et al*, 1988). Such intervention should only be a last resort, however, given that spontaneous resolution usually occurs over time.

Most commonly, dysosmias reflect a partially damaged olfactory epithelium induced by upper respiratory infections, head trauma, nasal/sinus disease, or other disorders. In the majority of cases, total anosmia is not present, implying that the dysosmia requires some intact peripheral olfactory neurons for expression. In rare cases, dysosmias reflect an experience of an 'aura', which represents an electrochemical phenomenon emanating from cortical level brain stimulation in conditions such as seizures or migraines (West and Doty, 1995; Acharya *et al*, 1998; Kelman, 2004). A current, likely oversimplified, explanation for an epileptic aura is that is represents a region of focal cortical excitation (simple partial seizure) and a migranous aura represents a nidus of glial cell-mediated spreading electrical depression. Patients who experience recurrent spontaneous olfactory hallucinations – such as a 'burning tire smell', 'putrid odor', or 'vomitus' – may actually be dealing with an epileptic or a migranous aura. History typically helps to elucidate the cause, like a secondary generalized seizure or development of a severe hemicranial headache syndrome. Of note, one of the most common presentations of brain tumors is a focal or secondarily generalized seizure. In many cases, aura-like dysosmias can be chronic or occur at regular intervals without producing evidence of seizure activity. Some psychiatric syndromes, including psychoses and the 'olfactory reference syndrome', are also associated with phantosmias or dysosmic episodes.

Although some patients complain of heightened sensitivity to odors, olfactory testing rarely validates the complaints. In fact, many persons with such complaints actually evidence, on olfactory testing, decreased, not increased, smell function. Documentation of hypersensitivity would require exceptional performance on olfactory tests (e.g., UPSIT scores of 40

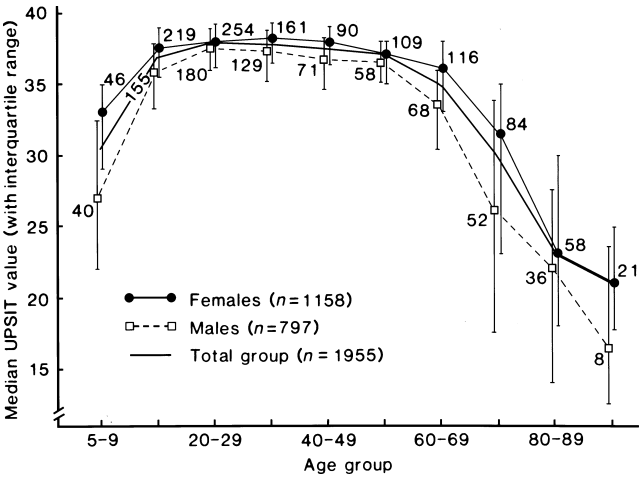

Figure 4 Scores on the University of Pennsylvania Smell Identification Test (UPSIT) as a function of age in a large heterogeneous group of subjects. Numbers by data points indicate sample sizes. From Doty *et al*, 1984, with permission. Copyright © 1984 The American Association for the Advancement of Science

and detection threshold values several orders of magnitude below normal). Although adrenal cortical insufficiency has been reported to be accompanied by hyperosmia (Henkin *et al*, 1967), as measured by threshold testing, this has not been conclusively documented. There is no evidence that persons with so-called multiple chemical sensitivity have heightened olfactory ability, as objectively measured (Doty *et al*, 1988a). Despite reports of hyperosmia in some temporal lobe epilepsy patients prior to an ictal event, most such patients generally have decreased olfactory function secondary to sclerosis within temporal lobe regions associated with the epileptic foci.

Some studies find a general association between the degree of smell loss and nasal disease severity. However, it is only in extreme cases of nasal obstruction, such as severe inflammation or polyposis, that a relationship can be documented between nasal airway patency, as measured by rhinomanometry, and olfactory dysfunction. Interestingly, quantitative measures of smell function rarely return to completely normal levels in patients with sinonasal disease (including polyposis) even after functional endoscopic sinus surgery or systemic steroid treatment, despite patient reports to the contrary (Doty and Mishra, 2001). Kern (2000) suggested that chronic inflammation is toxic to olfactory neurons and hypothesized that lymphocytes, macrophages, and eosinophils release inflammatory mediators that in turn enhance the apoptotic process by up-regulating the critical enzymes (e.g., Caspase 3). In support, several studies have shown absent or atrophic olfactory epithelium in nasal mucosal biopsies of anosmic patients (Hasegawa *et al*, 1986; Jafek *et al*, 1990).

A common misconception in cases of head trauma is that the region of the cribriform plate must be fractured or show pathology for smell loss to be present. In fact, fractures through the region of the cribriform plate are not required; a blow to the head that results in rapid acceleration or deceleration of the brain relative to the skull can sever or damage the very thin olfactory fila as they course between the nasal and brain cavities. A strange odor, likely representing either regeneration or degeneration of the receptor neurons, is often noticed for a few weeks or a month after such injuries. Olfactory dysfunction occurs more frequently from blows to the back than to the front of the head, in part because frontal blows are cushioned to some degree by the collapse of soft facial structures (e.g., the nose and sinuses) (Doty *et al*, 1997b). In terms of iatrogenesis other than chemical exposures, causes of olfactory disturbance are generally related to surgical interventions involving such regions as the olfactory cleft, cribiform plate, anterior skull base, and subfrontal regions of the brain near the olfactory bulb and related structures (Murphy *et al*, 2003). Trauma-related iatrogenic causes of *gustatory* dysfunction include surgical interventions near the chorda tympani and glossopharyngeal nerves (Bromley and Doty, 2003). The chorda tympani is at risk during procedures that may involve the middle ear, such as tympanoplasty, mastoidectomy, or stapedectomy. The lingual branch of the glossopharyngeal nerve sits in close proximity to the palantine tonsillar bed, thus making it susceptible to procedures such as tonsillectomy, bronchoscopy, and laryngoscopy. Third molar extractions, particularly those with deep impaction, are famous for potentially leading to gustatory disturbance that can last for many months after the extraction (Shafer *et al*, 1999).

The dental practitioner should be sensitive to the fact that decreased smell function (and potential complaints of flavor disturbance) may be a result of exposure to medications. Although gustatory function is typically affected more frequently, both smell and taste are susceptible to deleterious effects of many commonly used medications (Doty *et al*, 2008). Frequently encountered offending medications include calcium-channel blockers, antibiotics, antidepressants, sleep-induction agents (i.e., Lunesta), thyroid medications, and some statins.

Airborne chemicals have also been reported to result in distortions or loss of smell function (Doty and Hastings, 2001; Antunes *et al*, 2007). Cigarette smoke is injurious to health, as it can have adverse effects on the oral cavity and olfactory system (Vellappally *et al*, 2007). In addition to cosmetic effects of staining teeth, it can make one susceptible to oronasal infections and cancer. While smoking itself rarely causes anosmia, smell loss is inversely related to the pack-years smoked (Frye *et al*, 1990). Chronic exposure to chemicals such as acrylates, styrene, solvent mixtures, and some metals e.g. cadmium, chromium, manganese, arsenic, mercury, and organic lead, have resulted in reports of diminished or distorted olfactory function, although reporting methods have varied substantially, making definitive comparisons difficult (Schwartz *et al*, 1989; Gobba, 2006). On a more personal note, the dentist or dental technician may be at risk for occupational exposure to a potential olfactory toxin in the form of methyl methacrylate (Schwartz *et al*, 1989; Leggat and Kedjarune, 2003). Methyl methacrylate is a self-polymerizing acrylic resin with a wide variety of dental, medical, and industrial applications. While not thought to be carcinogenic to humans under normal use, potential olfactory toxicity may occur (Braun *et al*, 2002). In patients who undergo radiation therapy for head and neck cancers, focused beam or whole brain radiation may result in temporary or permanent impairment of smell and/or taste (Fischer and Epstein, 2008). Chemotherapeutic agents are famous for their adverse effects on these senses (Mirza *et al*, 2008). Xerostomia is a side effect of radiation therapy and chemotherapy, and can directly influence the local chemical environment of the nasal and oral cavities.

A number of neurodegenerative disorders that are associated with smell impairment may occasionally result in complaints of chemosensory disturbance by the dental patient. Examples include Parkinson's disease (PD), dementia of the Alzheimer's Type, and multiple sclerosis (Hawkes and Doty, 2009). Observation and recognition of related clinical features may help a seasoned clinician direct a patient for further treatment by a specialist (i.e., neurologist, geriatrician,

internist, etc.). In PD, impairment in olfactory detection, identification, and discrimination has been shown generally to occur before the classic motor features of the condition appear, often predating a clinical diagnosis of PD by at least 4 years (Ross *et al*, 2008). While smell and taste complaints are generally uncommon in AD patients, identifiable deficits are universally present and can contribute to nutritional deficiencies and illness (Doty, 2003). It appears that olfactory function in multiple sclerosis varies as a function of exacerbation and remission of plague activity, with lesions in the frontal and temporal regions having more of an impact (Doty *et al*, 1997a, 1999; Zorzon *et al*, 2000).

Of particular interest to the dental professional is the commonly encountered condition of halitosis. Bad breath emanating from the oral cavity appears to affect as many as one in four adults and seems to be related to volatile sulfur compounds that are released secondary to bacterial breakdown of proteins (Haraszthy *et al*, 2007; Whittle *et al*, 2007). In the vast majority of cases, it seems that the halitosis comes from inadequate plaque control, excessive growth of bacteria on the back of the tongue, periodontal disease, or dry mouth. If extreme, halitosis can influence chemosensory function in addition to resulting in uncomfortable social circumstances.

Clinical evaluation

A comprehensive discussion of a thorough clinical evaluation is beyond the scope of this paper, but a brief account of main investigations is mentioned. For accurate assessment of any patient with a chemosensory dysfunction, a detailed clinical history, a thorough physical examination including ORL and neurological assessments, and specialized investigations need to be carried out apart from the aforementioned olfactory quantification. For many patients, more specific evaluation may be necessary and often includes the following procedures (Bromley, 2000):

1. Neuroimaging: High resolution Computed Tomography (CT) appears to be the most useful and cost-effective screening tool for the assessment of sinonasal tract inflammatory disorders. Bony architecture is well-delineated with CT imaging. The nasal cavity, paranasal sinuses, hard palate, anterior skull base, orbits, and nasopharynx should be scanned and if central causes of olfactory dysfunction are suspected, the brain as well. Coronal sections are particularly valuable for the paranasal anatomy, including the anterior nasoethmoid (ostiomeatal) region (i.e., the maxillary sinus ostium, infundibulum, uncinate process, and middle meatus). For identification of vascular lesions, tumors, abscess cavities, and meningeal or parameningeal processes, intravenous enhancement is frequently employed. Magnetic Resonance Imaging (MRI) is the modality of choice for evaluation of soft tissue, including the olfactory bulbs, olfactory tracts, and parenchymal lesions in and around the brain. MRI has utility in distinguishing solid enhancing tumors from rim-enhancing inflammatory processes. The other imaging techniques for evaluation of central causes include functional MRI, positron emission tomography, magnetoencephalography and single photon emission computed tomography scanning (Li *et al*, 2003).
2. Blood analysis: Depending on the suspected condition, a more extensive serum analysis may be necessary. On a basic level, a complete blood count and erythrocyte sedimentation rate may help to identify infective, nutritional, or inflammatory processes involved in smell dysfunction. A screen of a chemistry panel, including electrolytes, blood urea nitrogen, creatinine, and blood glucose, can help to reveal renal disease or diabetes (among other conditions). Thyroid function studies, liver function studies, specific vitamin levels (i.e., B1, B12, E), and allergy testing may be of value.
3. Nasal secretions/fluid analysis: Occasionally, serous discharge can be examined for CSF (CSF rhinorrhea) if disruption of the cribiform plate is suspected. Also, mucopurulent discharge can be subjected to microscopic examination with cultures sensitive to bacteria to rule out local infection.
4. Mucosal biopsies: Rarely, a biopsy may be undertaken by an experienced surgeon to document cellular changes at neuroepithelial level, particularly if neoplasm is suspected. In such cases, a small piece of olfactory mucosa is typically stripped along the nasal septum by an endoscopic approach (Lovell *et al*, 1982; Lanza *et al*, 1993). However, this approach has limitations, most notably sampling issues (Paik *et al*, 1992).
5. Neuropsychological assessment: Cognitive assessment has a utility in patients where the central nervous system processes may be present as a cause for their chemosensory complaints (e.g., Alzheimer's disease, Parkinson's disease, multiple sclerosis, etc.). One commonly used brief office-based screen is the Mini-Mental State Examination, which can justify further neurocognitive evaluation and also be used as a monitoring tool (Folstein *et al*, 1975). Other more specific neuropsychological instruments can be used and referral to a neuropsychologist may be necessary.
6. Additional testing: Occasionally, it is necessary to perform an electroencephalogram (EEG), particularly in the context of spontaneous olfactory or gustatory hallucinations/auras. Cerebrospinal fluid analysis (via lumbar puncture) can also be of benefit when conditions such as multiple sclerosis, dementia, or central nervous system infections are being considered.

Management of olfactory disturbance

Depending on the presumed mechanism of olfactory disturbance, there are a number of specific therapies which may be of benefit. It is well-known that systemic

medical conditions, such as hypothyroidism, diabetes, and infection, can have an adverse effect on neural function. Such conditions may contribute to aberrant olfactory neural transduction and, therefore, should be looked for and, when present, corrected. Obstructive lesions – such as polyps or other intranasal lesions – are best managed by an otolaryngologist as many of these patients need endoscopy and/or surgical interventions. However, in the case of intranasal and sinus-related inflammatory conditions, the use of intranasal or systemic steroids can be helpful. A common regimen of oral steroid involves a taper from 60 mg down to 0 mg over 2 weeks. If smell function significantly improves, then continued management with intranasal steroids can be attempted. Intranasal steroids are typically more effective if Moffett's position is used for administration (head in the inverted position, such as over the edge of the bed, with the bridge of the nose perpendicular to the floor). Moffett's position facilitates penetration of the nasal steroid into the olfactory meatus and cleft. Short-term use of intranasal decongestants may also be of benefit in some circumstances where nasal congestion is excessive and clearly obstructive. In specific cases of head injury resulting in hyposmia, an initial trial of steroids is recommended in most circumstances. This may help to reduce local edema and potential deleterious deposition of scar tissue around the olfactory neurons (particularly at the level of the cribiform plate) (Jafek and Hill, 1989).

A recent report suggests that some patients with hyposmia may benefit from smelling strong odors, e.g., eucalyptol, citronella, eugenol, and phenyl ethyl alcohol, several times on a daily basis over the course of 12 weeks (Hummel *et al*, 2009). Although this non-blinded study of a relatively small number of patients who self-administered the odorants is suggestive, double-blind studies are needed to establish definitively whether such 'practice' has efficacy. It is well-established that prolonged exposure to odorants can induce increased neural activity in young rodents within central brain structures, most notably the olfactory bulb (Coopersmith and Leon, 1984; Coopersmith *et al*, 1986; Woo *et al*, 2006, 2007), and in humans some increase in threshold sensitivity can occur following repeated exposure to some odorants (Doty *et al*, 1981; Wysocki *et al*, 1989).

There are a number of dietary supplements discussed in the literature as potentially beneficial in supporting proper neuronal function, including olfactory nerve function and regeneration. Alpha-lipoic acid – an over-the-counter antioxidant – has been reported to be of value in mitigating smell loss (Hummel *et al*, 2002), although double-blind studies are still lacking. Daily use of zinc and vitamin A has been suggested to be of value, although their influences are likely present only in the context of established deficiencies. Most notably, a double-blind study of the efficacy of zinc was found to be negative (Henkin *et al*, 1976). Retinoids (bioactive vitamin A derivatives) are known to play an essential role in the survival of olfactory neurons (Hagglund *et al*, 2006). In a time where irritable bowel syndrome, Crohn's disease, and other primary GI disturbances are common, it is important to look for relative B12 deficiency. B12 is absorbed in the small bowel with the help of gastric-produced intrinsic factor. Frank B12 deficiency can result in neuronal dysfunction at the level of the peripheral nerve, spinal cord, and brain, and can theoretically contribute to olfactory nerve disturbance. The use of B2 (riboflavin) and magnesium are now considered essential in the alternative literature for the management for migraine (Sun-Edelstein and Mauskop, 2009). Interestingly, magnesium helps to stabilize the neuro-excitatory glutamate-based NMDA receptor naturally, thereby decreasing neuronal hyperexcitability.

In some cases, antiepileptic or antidepressant medications have been used with some success in ameliorating olfactory complaints. With olfactory auras and possibly dysosmias, the antiepileptic medication gabapentin (Neurontin) may help, although empirical evidence for such aid is lacking. Gabapentin is a calcium channel subunit modulator that helps to stabilize neuronal transduction and prevent neuronal hyperexcitation. In theory, this antiepileptic medication helps to suppress epileptic events and 'calm' peripheral nerve structures that mediate neuropathic pain or other aberrant experiences (paresthesias/dysasthesias). Currently, gabapentin has indications for conditions such as partial seizures and trigeminal neuralgia. A newer and more potent version of this medication (in the same pharmaceutical class) is pregabalin (Lyrica). Pregabalin has FDA-approved indications for conditions such as partial seizures, painful diabetic peripheral polyneuropathy, postherpetic neuralgia, and fibromyalgia, and – like gabapentin – may help to 'calm' neuronal hyperexcitation. The antidepressant amitriptyline (Elavil) is a commonly used medication that can help with depressed mood, neuropathic pain, and facilitate sleep induction. This medication is often used for dysosmias and smell distortions, particularly after head trauma. Ironically, amitriptyline is frequently on the list of medications that can also ultimately distort taste function, possibly from its potential anticholinergic/drying effects (Doty *et al*, 2008). Psychotherapy, particularly in the form of cognitive-behavioral therapy, may be beneficial to some patients with primary mood disturbance or postconcussive syndrome.

Just as proper oral hygiene is a mainstay of dental management, proper intranasal hygiene is also important. Excessive picking and plucking at the level of the nasal muscosa must be avoided. Additionally, the chronic use of intranasal therapies (e.g., antimigraine triptan medications) and illicit drugs (e.g., cocaine) may distort or even damage normal olfactory nerve function. Breathing activities or oxygenation devices (e.g., CPAP for obstructive sleep apnea) that result in drying of the olfactory mucosa should be either changed or reconfigured to include humidification.

Conclusions

The oral health specialist may frequently encounter patients with complaints of 'taste problems.' Indeed, primary problems within the oral cavity can result in

gustatory distortions; however, this review acknowledges that most patients presenting with 'taste loss' typically have olfactory, rather than gustatory, dysfunction. Questions for such patients should emphasize the patient's ability to detect and distinguish primary taste sensations such as sweet (sugar), sour (grapefruit), salt (pretzels), and bitter (coffee), as this will help to clarify whether the problem is gustatory in nature. In addition to a detailed examination of the oral cavity and dentition, an investigation of 'taste disturbance' should also include tests of smell function. In this paper, we reviewed an approach to executing this while discussing the multitude of processes which can affect olfaction. Recognizing the primary cause of the patient's taste (and ultimately smell) complaints can save a patient a tremendous amount of time and money being evaluated and managed. This being said, the realm of the dentist is more than simply the tongue and the oral cavity – in many cases, it also includes the nose.

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R.L.D. is President and major shareholder of Sensonics, Inc., a manufacturer and distributor of tests of taste and smell.

Author contributions

Bromley and Doty equally contributed to the writing of this review.

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