

The Olfactory System and Its Disorders

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ABSTRACT

The sense of smell is greatly underappreciated, despite the fact that it monitors the intake of airborne agents into the human respiratory system and determines to a large degree the flavor and palatability of foods and beverages. In addition to enhancing quality of life, this primary sensory system warns of spoiled foods, leaking natural gas, polluted air and smoke, and mediates basic elements of communication (e.g., mother–infant interactions). It is now apparent that smell dysfunction is among the first clinical signs of such neurodegenerative diseases as Alzheimer's disease and sporadic Parkinson's disease. In this brief article, the author reviews the anatomy and physiology of this primary sensory system, means of assessing its function, and major diseases and disorders with which it is intimately associated.

KEYWORDS: Smell, olfaction, anosmia, dysosmia, Alzheimer's disease, Parkinson's disease, aging

Although neglected by the medical community at large, olfaction is critically important for safety, nutritional status, and quality of life; its dysfunction is now known to be among the earliest “preclinical” signs of Alzheimer's disease (AD) and sporadic Parkinson's disease (PD).^{1–6} Among 750 consecutive patients presenting to the University of Pennsylvania Smell and Taste Center with chemosensory complaints, 68% experienced an altered quality of life, 46% changes in appetite or body weight, and 56% adverse influences on daily living or psychological well-being.⁷ In another study of 445 patients with complaints of chemosensory disturbance, at least one hazardous event, such as food poisoning or failure to detect fire or leaking natural gas, was reported by 45.2% of those with anosmia, 34.1% of those with severe hyposmia, 32.8% of those with moderate hyposmia, 24.2% of those with mild hyposmia, and 19.0% of those with normal olfactory function.⁸

Most complaints of decreased “taste” function actually reflect decreased smell function.⁷ Such flavors as coffee, chocolate, vanilla, strawberry, pizza, licorice, steak sauce, root beer, and cola are dependent upon stimulation of cranial nerve (CN) I from volatiles that

enter the nasal pharynx during deglutition.⁹ These sensations disappear when the olfactory epithelium is markedly damaged, leaving intact only somatosensory sensations and the perception of the primary taste qualities of sweet, sour, salty, bitter, metallic, and umami (monosodium glutamate–like). Whole-mouth taste function is much more resilient to pathologic or trauma-related alterations than is smell function, in large part because of the redundant innervation of the taste buds from several cranial nerves (i.e., CN VII, IX, and X).⁷

In this article the anatomy and physiology of the olfactory system is reviewed, as well as means for assessing its function and disorders in which it is intimately involved. Emphasis is placed on disorders commonly encountered by the practicing neurologist.

ANATOMY AND PHYSIOLOGY

Sensory Receptors and Primary Neurons

The peripheral elements of the olfactory system consist of ~6 million bipolar receptor cells whose cell bodies, dendrites, and initial axon segments are located within

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the olfactory neuroepithelium in the roof of the nasal chamber.¹⁰ This pseudostratified columnar epithelium is supported by a highly vascularized lamina propria covering the cribriform plate, the superior septum, and sectors of both the superior and middle turbinates.¹¹ The receptor cell axons project through the cribriform plate of the ethmoid bone and synapse within the glomerular layer of the olfactory bulb after forming into bundles—the olfactory fila. Receptor-bearing cilia, numbering from 3 to 50 per cell, project from the dendritic ends of the receptor cells into the overlying mucus, in some cases radiating over 30 μm . In the human, the surface area of the cilia is $\sim 25 \text{ mm}^2$.¹²

The bipolar receptor neurons are unique in several ways. First, they can regenerate from basal cells after being damaged. Second, each cell serves as both a receptor cell and a first-order neuron, projecting an axon directly from the nasal cavity into the brain without an intervening synapse. Their rather direct exposure to the external environment, along with their large surface area and minimal xenobiotic-metabolizing capacity, make them a primary route of invasion into the brain of several xenobiotic agents. Indeed, many neurovirulent viruses are capable of penetrating the brain via the olfactory receptor cells.¹³ Finally, such cells are highly specialized, individually expressing receptors that respond to only certain elements of odorant ligands.¹⁴

The initial step in olfactory transduction is the movement of odorants from the air phase of the nasal cavity into the aqueous phase of the olfactory mucus. Odorants, most of which are hydrophobic, then diffuse or are transported through the aqueous medium to olfactory receptor proteins of the cilia, ultimately inducing action potentials in the receptor cells.¹⁵ Although several odorants stimulate free nerve endings from CN V and some other cranial nerves distributed in the nasal mucosa, nasal pharynx, or oral cavity, such stimulation primarily involves somatosensory sensations of the “common chemical sense,” such as warmth, coolness, pungency, and irritation.¹⁶

There is marked genetic diversity in olfactory receptors. A large multigene rodent family of ~ 1000 genes appears to code for odorant receptor proteins with seven transmembrane domains.¹⁷ In humans, more than half of this receptor gene family are pseudogenes, indicating that the number of functional receptors is less than 500.¹⁸ Even though each receptor cell expresses only one type of olfactory receptor, such cells respond to a wide range of odorants. However, a given receptor, though a “generalist,” does not respond to all stimuli to which another receptor responds, thereby allowing for cross-neuron quality coding.¹⁴

The olfactory receptors cells are physically isolated from one another within the olfactory neuroepithelium by sustentacular or supporting cells.¹¹ The latter cells secrete mucopolysaccharides into the mucus, detox-

ify and degrade odorants, and transport some molecules across the epithelium. However, most of the mucus that covers the surface of the olfactory epithelium comes from Bowman's glands, specialized glands found only within the olfactory epithelium. Among other cell types within this epithelium are basal stem cells (the precursors of all of the main types of cells of the epithelium) and the poorly understood microvillar cells, which number $\sim 600,000$ in humans and send tufts of microvilli into the nasal mucus.¹⁰

Olfactory Bulbs and Their Projections

Each ovoid olfactory bulb is located at the base of the frontal lobe overlying the cribriform plate of the ethmoid bone. The olfactory bulbs are composed of neurons, afferent and efferent nerve fibers, multiple interneurons, microglia, astrocytes, and blood vessels, all surrounded by a thin layer of pia-arachnoid cells.¹⁹ The bulb's cellular elements are arranged in six concentric layers: the olfactory nerve layer, the glomerular layer, the external plexiform layer, the mitral cell layer, the internal plexiform layer, and the granule cell layer. The latter layer makes up about half the volume of the entire bulb.

The receptor cell axons synapse within the spherical olfactory bulb glomeruli, which are arranged in single or double layers. These structures number in the thousands in younger persons and are a defining feature of the olfactory system. With age, however, the number and integrity of the glomeruli greatly decrease, being nearly absent in elderly persons.²⁰ The development and maintenance of the glomeruli depend on trophic influences exerted by the receptor cells. Because a given receptor cell projects to only one or two glomeruli, the glomeruli are, in effect, functional representations of the receptor types.¹⁴

The main second-order neurons, which are the primary output neurons of the bulb, are the mitral and tufted cells. The apical dendrites of these cells are influenced not only by the olfactory nerve terminals, but also by interneurons and centrifugal fibers, most of which are GABAergic or dopaminergic.²¹ Several bulbar interneurons, including the granule cells, are replaced by progenitors germinating within the subventricular zone of the brain. These cells migrate along the rostral migratory stream to the olfactory bulb.²²

Olfactory Cortex

The mitral and tufted cell axons leave the bulb via the lateral olfactory tract to synapse on structures collectively termed the primary olfactory cortex, including the anterior olfactory nucleus (AON), the piriform cortex, the anterior cortical nucleus of the amygdala, the periamygdaloid complex, and the rostral entorhinal cortex. The components of the olfactory cortex have rich

(and reciprocal) relationships with one another and several higher brain structures. For example, the entorhinal cortex supplies afferent fibers along the entire length of the hippocampus. The axons of the pyramidal cells of the AON, whose sectors lie within the posterior segment of each bulb and the rostral part of the olfactory peduncle, project to ipsilateral and contralateral (via the anterior commissure) rostral olfactory brain structures, playing a significant role in the regulation of neural input to the two sides of the brain.²³ Although the olfactory system is unique among sensory systems in sending fibers directly to cortical regions without synapsing in the thalamus, connections between the primary olfactory cortex (e.g., entorhinal cortex) and secondary olfactory cortex (e.g., orbitofrontal cortex) do occur via the dorsal medial thalamus.

In general, the piriform cortex encodes higher-order representations of odor quality, identity, and familiarity, and is associated with the learning and remembering of odors, as well as coordinating information between olfaction, vision, and taste.²⁴ The amygdala is believed to respond only to the intensity of emotionally significant, i.e., pleasant or unpleasant odors. The entorhinal cortex preprocesses information entering the hippocampus, being intimately involved in learning and memory.²⁴ The caudal orbitofrontal cortex has been associated with odor detection, whereas the more rostral regions are involved in working memory, associative learning, and short- and long-term odor recognition memory.²⁴ The medial orbitofrontal cortex and ventromedial prefrontal cortex are activated by pleasant odors, whereas the lateral orbitofrontal cortex and neighboring inferior prefrontal cortex are activated by unpleasant odors.²⁵ This medial:lateral responsiveness to pleasant and unpleasant stimuli occurs for other senses as well, implying that these regions are important for general sensory hedonistic processing.

TESTS OF OLFACTORY FUNCTION

Accurate olfactory assessment is essential to (1) establish the validity of a patient's complaint; (2) characterize the specific nature of the problem; (3) reliably monitor changes in function over time, including those resulting from medical interventions or treatments; (4) detect malingering; and (5) establish compensation for permanent disability. Several patients who present with complaints of anosmia or hyposmia actually have normal function relative to their peers. Others are unaware of their dysfunction. In the case of PD, for example, ~90% of patients have a demonstrable olfactory loss, yet less than 15% are aware of the problem until being tested.

Electrophysiologic, psychophysical, and psychophysiologic tests are available for assessing smell function.^{26,27} The most practical are psychophysical tests of odor identification and detection. The most widely used

odor identification test, the University of Pennsylvania Smell Identification Test [UPSIT; known commercially as the Smell Identification TestTM (Sensonics, Inc., Haddon Heights, NJ)], was developed at our center and can be self-administered in 10 to 15 minutes by most patients in the waiting room and scored in less than a minute by nonmedical personnel.²⁸ This 40-item test, along with its briefer clones, is available in numerous languages and has been employed in hundreds of clinical and experimental studies. In this test, a patient is presented with 40 "scratch and sniff" odorant pads and is required to choose, from four response alternatives, an answer for each stimulus, even if none seems appropriate or no odor is perceived. This encourages careful sampling of the stimuli and provides a means for detecting malingering. Because chance performance is 10 out of 40, very low scores reflect avoidance, and hence recognition, of the correct answer. Norms based on responses from nearly 4000 people are provided, and an individual's percentile rank is established relative to persons of the same age and gender. Olfactory function can also be classified, on an absolute basis, into one of six categories: normosmia, mild microsmia, moderate microsmia, severe microsmia, anosmia, and probable malingering.

Threshold olfactory tests typically employ a dilution series of a stimulus in an odorless diluent, such as light mineral oil. In most clinical applications, the stimuli are presented via small sniff or squeeze bottles, or felt-tipped pen-like devices, using a series of ascending or descending concentration trials. As with odor identification tests, forced-choice response between odorant and blank trials is required. The reader is referred elsewhere for details on the various procedures used in assessing human olfactory thresholds.²⁹

Despite the fact that bilateral testing detects most clinically meaningful cases of olfactory dysfunction, unilateral testing can detect deficits that are not ordinarily recognized. In general, bilateral tests measure the functioning of the better side of the nose.³⁰ To assess unilateral function, the naris contralateral to the tested side is occluded to prevent or minimize crossing of inhaled or exhaled air at the rear of the nasopharynx to the opposite side (so-called retranasal stimulation). In our clinic, we achieve this end by sealing the naris contralateral to testing using a piece of 3M Microfoam[®] tape (3M Corp, Minneapolis, MN) cut to fit its borders. The patient is instructed to sniff the stimulus normally and to exhale through the mouth.

TYPES OF OLFACTORY DYSFUNCTION

Olfactory dysfunction can be total (i.e., anosmia) or incomplete (e.g., partial anosmia, hyposmia, or microsmia). It can also reflect distortions (dysosmias; e.g., a rotten-like smell when sniffing a rose) or spontaneous sensations (phantosmias; e.g., the presence of a smell

when no stimulus is present). Inability to recognize odors may occur independently of a normally functioning olfactory system (olfactory agnosia). Hyperosmia is a rare condition of abnormally acute smell function. As with vision or hearing, olfactory dysfunction can be either bilateral or unilateral (sometimes termed binasal or uninasal). Thus, if a person has anosmia on the left side of the nose but not the right, the condition is described as unilateral left anosmia. Anosmia that is present on both sides of the nose is termed bilateral anosmia or total anosmia.

Some complaints of dysosmia reflect the production of foul odors within the nasal cavity (e.g., as a result of bacterial infection) or within the body proper (e.g., as a result of altered metabolism). Although the basis of several such problems has nothing to do with alterations in the olfactory pathway, the term dysosmia is still used for describing the complaint.

CAUSES OF OLFACTORY DYSFUNCTION

Many factors, including diseases, influence the normal ability to smell. Nearly two-thirds of all chronic anosmia or hyposmia cases are due to prior upper respiratory infections, head trauma, and nasal and paranasal sinus disease that damage the olfactory neuroepithelium.⁷ Additional factors that can influence olfactory function include age, sex (women are generally more sensitive than men), smoking behavior, neurodegenerative diseases, iatrogenic interventions (e.g., septoplasty, rhinoplasty, turbinectomy, radiation therapy), intranasal neoplasms (e.g., papillomas, hemangiomas, and ameloblastomas), intracranial tumors or lesions (e.g., Foster Kennedy syndrome, olfactory groove meningiomas, frontal lobe gliomas), epilepsy, psychiatric disorders, exposure to toxic chemicals, hypothyroidism, renal disease, and kidney disease.³¹ The more common influences are described in detail below.

Age

Decreased smell function occurs in the “normal” elderly. In fact, age is the strongest correlate of olfactory decline in healthy adult humans, having a much larger impact than even cigarette smoking.²⁸ Generally, age-related decline in olfactory function is more severe for men than for women, although marked individual differences are present. Unlike alterations in hearing and vision, age-related changes often go unnoticed, and smell ability is rarely evaluated clinically. Under 65 years of age, ~2% of the population has chronic problems smelling. Between 65 and 80 years, this rises dramatically, with about half of the population experiencing significant decrements in the ability to smell. Over the age of 80, this figure rises to nearly 75%.²⁸ The basis for age-related changes in smell function are multiple and include, among other things,

ossification and closure of the foramina of the cribriform plate,^{32,33} development of early neurodegenerative disease pathology,^{34,35} and cumulative damage to the olfactory receptors from repeated viral and other insults throughout life.³⁶

Viral Infections

Upper respiratory infections, usually viral in nature, are the most common cause of permanent hyposmia or anosmia.^{7,31} Such dysfunction, unlike that related to nasal inflammatory disorders, exhibit no fluctuations over time and, in some cases, can reflect damage not only to the olfactory epithelium, but to central olfactory structures as a result of viral invasion into the brain. Among virus-related disorders capable of damaging the olfactory neuroepithelium are the common cold, hepatitis, flu-like infections, and herpes simplex encephalitis.³⁷ Polio, the Indiana strain of wild-type vesicular stomatitis, rabies, herpes simplex types 1 and 2, mouse hepatitis, herpes suis, Borna disease, and canine distemper viruses are all known to be neurotropic for peripheral olfactory structures.³⁸ Increased susceptibility to viral damage can occur from reduction or inhibition of mucociliary transport by disease, drugs, diet, or genetic factors, as well as from age-related changes in nasal function and normal defense mechanisms.³⁹

Most viral infections are either entirely asymptomatic or so mild as to go unrecognized, as evidenced by the fact that during seasonal epidemics the number of serologically documented influenza or arboviral encephalitis infections exceeds the number of acute cases by several hundredfold.³⁷ Hence, many unexplained cases of smell dysfunction likely reflect unrecognized viral infections. On rare occasions, smell dysfunction has been associated with influenza vaccines in a manner likely analogous to vaccine-related cases of Bell's palsy and Guillain-Barré syndrome.⁴⁰ However, the number of such cases is apparently low and coincidental viral infection cannot be excluded from consideration.

Some viruses that are not ordinarily neurotropic may become so after entering the nose. The NWS strain of influenza virus, for example, typically spreads perivenously when injected intraperitoneally into mice and viral antigen is restricted to the meninges, choroid plexus, ependymal cells, and perivascular locations within the brain parenchyma. However, when inoculated into the nose, this virus can spread through the olfactory and trigeminal nerves and invade the brain.⁴¹

Exposure to Toxic Chemicals and Nanoparticles

Exposure to several airborne toxins, including herbicides, pesticides, solvents, and heavy metals, can alter the ability to smell, particularly when such exposure has been chronic.⁴² Among the heavy metals, the best

documented cases are for cadmium, chromium, nickel, and manganese. In addition to damaging the olfactory epithelium, such agents, as well as viruses, nanoparticles, and prions likely enter the brain via the olfactory mucosa. Animal studies have shown that the olfactory receptor neurons can take up and transport cadmium, gold, and manganese ions toward the olfactory bulbs at rates ranging from 2.5 to 3 mm/hour.^{43–45} There is epidemiologic and other evidence that some airborne toxins may be involved in the etiology of neurodegenerative disease.¹³

Epilepsy

Early threshold studies of patients with epilepsy reported heightened, not lessened, overall bilateral sensitivity, particularly prior to an ictal event.⁴⁶ More recent work has generally found normal thresholds, although this may reflect the influence of antiseizure medications.⁵ Suprathreshold deficits are common in epilepsy, with right-side foci seemingly being more disrupting. Thus, epileptic patients with right-sided foci, but not left-sided foci, have been found to exhibit decreased performance on an odor-matching task,⁴⁷ an odor-memory test for nameable odors,⁴⁸ and the UPSIT.⁴⁹ Bilateral deficits have been reported for odor discrimination, short- and long-term odor memory, and odor naming.⁵⁰ Prolonged odor event-related potential latencies have been reported in patients with both right- and left-sided foci when the stimulation was made on the side with the epileptic focus.⁵¹

Neurodegenerative Diseases

Of particular relevance to the neurologist is the observation that olfactory dysfunction is a cardinal feature of several neurodegenerative diseases such as AD and PD. Surprisingly, most AD and PD patients are unaware of their olfactory deficit prior to testing. In both of these diseases, the deficit is present in 85 to 90% of early-stage patients and is associated with decreased activation of central odor processing structures (as measured by functional imaging). The deficit associated with PD does not respond to anti-PD medications (e.g., L-dopa, dopamine agonists, anticholinergic compounds), and occurs as severely in nonmedicated or never-medicated patients as in medicated ones.^{52–54} Moreover, its magnitude is not associated or is very weakly associated with disease stage, the severity of motor symptoms, or scores on neuropsychologic tests, such as the verbal and performance subtests of the Wechsler Adult Intelligence Scale.^{52,55} In one study, the sensitivity and specificity of olfactory testing in differentiating between controls and early-stage clinically diagnosed PD patients was 0.91 and 0.88, respectively, in males ≤ 60 years of age).⁵⁶

There is now evidence that smell loss may precede the classical symptoms of AD and PD by several years, reflecting the so-called preclinical period. Otherwise normal persons who are anosmic and possess the apolipoprotein E-4 (APOE-4) allele have 4.9 times the risk of having future cognitive decline than those who do not possess the genetic marker.² In a study of 361 relatives of PD patients, those scoring in the lowest (hyposmic) and highest (normosmic) deciles of an olfactory test battery underwent dopamine transporter imaging.⁵⁷ At the 2-year follow-up, 10% (4/40) of the hyposmic relatives, who also had a substantial reduction in [¹²³I]β-CIT uptake at baseline, had developed clinical PD, while none of the 38 normosmic relatives developed PD or had an abnormal reduction in [¹²³I]β-CIT binding. The remaining nonparkinsonian hyposmic relatives exhibited a significantly greater average decline in dopamine transporter binding across the two tests than the nonhyposmic relatives, implying PD-related pathology was developing. These results suggest that olfactory dysfunction in first-degree relatives of PD patients is associated with at least a 10% increased risk for developing clinically defined PD within 2 years and are in accord with findings that the olfactory bulbs are among the first brain regions to exhibit PD-related neuropathology.^{58,59}

It is important to point out that there is considerable variation in the prevalence and magnitude of olfactory dysfunction among neurodegenerative diseases. For example, the average olfactory dysfunction of AD, PD, and the Parkinson–Dementia Complex of Guam (PDG) is severe (UPSIT scores ~ 20), whereas that of Huntington's disease, multiinfarct dementia, amyotrophic lateral sclerosis, and schizophrenia is more moderate.^{60–63} Progressive supranuclear palsy (PSP) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonism (MPTP-P) are associated with only minor, if any, changes in the ability to smell, despite the fact that they share major clinical features with PD.^{64,65} Such findings have led to the suggestion that olfactory testing may aid in the differential diagnosis of several neurodegenerative diseases.^{66,67}

Neurodegenerative diseases with well-established genetic determinants are also associated with olfactory dysfunction. For example, such dysfunction is present in some individuals with familial PD^{68,69} and in individuals with Down syndrome (DS).^{70,71} The DS-related dysfunction is unlikely secondary to the AD-like neuropathology associated with this disorder because it occurs at an age before AD-pathology is manifest.⁷¹ Moreover, non-DS retarded children of the same IQ also exhibit such dysfunction. Thus, the olfactory loss may be associated with retardation, rather than AD-like amyloid pathology, per se.⁷¹

Another genetically determined disorder, Huntington's disease (HD), is associated with deficits in odor identification, detection, discrimination, and

memory. The problem is manifest by the time the classic phenotypic elements of the disorder appear, although it is unknown how far in advance the olfactory loss precedes the phenotypic expression. In one study, identification and detection threshold test scores were obtained from 25 probands with HD, 12 genetically at-risk offspring, and 37 unrelated controls. Decreased olfaction was noted only in the HD group.⁶² These findings were extended by testing 20 HD patients who had the disease for a mean of 8.0 years (range: 4 to 14 years), 20 normal subjects with the genetic mutation that causes HD, and 20 mutation-negative adults.⁷² Again, only the patients with clinical signs of HD exhibited depressed olfaction.

It is noteworthy that patients with multiple sclerosis exhibit olfactory dysfunction proportional to plaque burden in the subfrontal and subtemporal lobes.⁷³ Such dysfunction waxes and wanes during periods of exacerbation and remission.⁷⁴ It is also of interest that some patients with variant Creutzfeldt-Jacob disease present with olfactory dysfunction associated olfactory tract involvement of the prion protein (PrP), lending some credence to the concept that the olfactory pathway may represent a route of infection and possible means of spreading the infection.^{75,76}

Head Trauma

Head trauma accounts for ~20% of all chemosensory disorders exhibited by patients who present to our Center.⁷ The incidence of trauma-related olfactory dysfunction in the general population probably lies somewhere between 4 and 15%.⁷⁷ The likelihood of having smell loss from head trauma directly relates to the severity of the trauma and whether strong acceleration/deceleration of the head occurred. In a detailed study of 179 head-injured persons, occipital and side impact caused most damage and frontal impact the least.⁷⁷ Skull fractures or fractures through the cribriform area are not a prerequisite for the smell loss. On average, when recovery occurs it usually happens within a year of the injury. A recent study suggests prognosis depends on the degree of olfactory dysfunction upon presentation and that some, albeit minor, return of function can occur over time.⁷⁸

Other Disorders

Smell loss has been reported in disorders associated with cerebellar degeneration (e.g., Friedreich's ataxia) and is a hallmark of schizophrenia, a disease commonly viewed as neurodevelopmental (for review, see Doty⁵). In some cases of migraine, smell loss seems to be present although in rare instances hyperacuity has been reported to occur between ictal episodes.⁷⁹ Hyperosmia is classically associated with pregnancy and hyperemesis gravidarum;

however, it is not clear whether this phenomenon reflects true hypersensitivity or simply reactivity.

Patients with apparent congenital anosmia usually lack or have hypoplasia of the olfactory bulbs and stalks. For example, in a study of 25 patients who presented to our center with apparent congenital anosmia, magnetic resonance imaging (MRI) revealed an absence or hypoplasia of olfactory bulbs and tracts in all instances.⁸⁰ Because viral infections early in life may lead to olfactory epithelial damage and atrophy of the olfactory bulbs, it is difficult in many cases to establish that the apparent congenital loss is, in fact, congenital. In other cases, congenital loss runs in families. Perhaps the best established genetic disorder associated with smell loss is Kallmann's syndrome, where dysplasia of the olfactory bulbs and hypothalamic/hypophysis axis is the norm, along with degeneration of the olfactory receptor cell axons, receptor cell neuronal immaturity, and the formation of intraepithelial neuromas.⁸¹

CONCLUSIONS

The sense of smell is greatly underappreciated by physicians and laypersons alike. Evidence that olfactory dysfunction is an early sign of such neurologic diseases as AD and PD makes a patient's sense of smell of direct relevance to the neurologist. In this article, the anatomy and physiology of this important sensory system was reviewed, as were means for its quantitative assessment and factors that adversely influence its function, including age, head trauma, epilepsy, viral infections, toxic exposures, and a range of neurodegenerative diseases. Particular attention was paid to those disorders most commonly encountered by the neurologist.

DISCLOSURE

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

REFERENCES

1. Wilson RS, Schneider JA, Arnold SE, Tang Y, Boyle PA, Bennett DA. Olfactory identification and incidence of mild cognitive impairment in older age. *Arch Gen Psychiatry* 2007;64:802-808
2. Graves AB, Bowen JD, Rajaram L, et al. Impaired olfaction as a marker for cognitive decline: interaction with apolipoprotein E epsilon4 status. *Neurology* 1999;53(7):1480-1487
3. Ross GW, Petrovitch H, Abbott RD, et al. Association of olfactory dysfunction with risk for future Parkinson's disease. *Ann Neurol* 2008;63(2):167-173
4. Devanand DP, Liu XH, Tabert MH, et al. Predicting conversion from mild cognitive impairment to Alzheimer's disease. *Biol Psychiatry* 2007;61(8):102S
5. Doty RL. Odor perception in neurodegenerative diseases. In: Doty RL, ed. *Handbook of Olfaction and Gustation*. 2nd ed. New York: Marcel Dekker; 2003:479-502

6. Swan GE, Carmelli D. Impaired olfaction predicts cognitive decline in nondemented older adults. *Neuroepidemiology* 2002;21(2):58–67
7. Deems DA, Doty RL, Settle RG, et al. Smell and taste disorders, a study of 750 patients from the University of Pennsylvania Smell and Taste Center. *Arch Otolaryngol Head Neck Surg* 1991;117(5):519–528
8. Santos DV, Reiter ER, DiNardo LJ, Costanzo RM. Hazardous events associated with impaired olfactory function. *Arch Otolaryngol Head Neck Surg* 2004;130:317–319
9. Burdach KJ, Doty RL. The effects of mouth movements, swallowing, and spitting on retronasal odor perception. *Physiol Behav* 1987;41(4):353–356
10. Moran DT, Rowley JC III, Jafek BW, Lovell MA. The fine structure of the olfactory mucosa in man. *J Neurocytol* 1982;11:721–746
11. Menco BPM, Morrison EE. Morphology of the mammalian olfactory epithelium: form, fine structure, function, and pathology. In: Doty RL, ed. *Handbook of Olfaction and Gustation*. 2nd ed. New York: Marcel Dekker; 2003:17–49
12. Doty RL, Bromley SM. Olfaction and taste. In: Crockard A, Hayward R, Hoff JT, eds. *Neurosurgery: The Scientific Basis of Clinical Practice*. London: Blackwell Science; 2000:347–365
13. Doty RL. The olfactory vector hypothesis of neurodegenerative disease: Is it viable? *Ann Neurol* 2008;63:7–15
14. Johnson BA, Leon M. Chemotropic odorant coding in a mammalian olfactory system. *J Comp Neurol* 2007;503:1–34
15. Pevsner J, Snyder SH. Odorant-binding protein: odorant transport function in the vertebrate nasal epithelium. *Chem Senses* 1990;15(2):217–222
16. Doty RL, Cometto-Muniz JE, Jalowayski AA, Dalton P, Kendal-Reed M, Hodgson M. Assessment of upper respiratory tract and ocular irritative effects of volatile chemicals in humans. *Crit Rev Toxicol* 2004;34:85–142
17. Buck L, Axel R. A novel multigene family may encode odorant receptors: a molecular basis for odor recognition. *Cell* 1991;65(1):175–187
18. Malnic B, Godfrey PA, Buck LB. The human olfactory receptor gene family. *Proc Natl Acad Sci U S A* 2004;101(8):2584–2589
19. Kratskin IL, Belluzzi O. Anatomy and neurochemistry of the olfactory bulb. In: Doty RL, ed. *Handbook of Olfaction and Gustation*. 2nd ed. New York: Marcel Dekker; 2003:139–164
20. Smith CG. Age incident of atrophy of olfactory nerves in man. *J Comp Neurol* 1942;77:589–594
21. Shepherd GM. Synaptic organization of the mammalian olfactory bulb. *Physiol Rev* 1972;52(4):864–917
22. Gritti A, Bonfanti L, Doetsch F, et al. Multipotent neural stem cells reside into the rostral extension and olfactory bulb of adult rodents. *J Neurosci* 2002;22(2):437–445
23. Brunjes PC, Illig KR, Meyer EA. A field guide to the anterior olfactory nucleus (cortex). *Brain Res Brain Res Rev* 2005;50(2):305–335
24. Gottfried JA, Deichmann R, Winston JS, Dolan RJ. Functional heterogeneity in human olfactory cortex: an event-related functional magnetic resonance imaging study. *J Neurosci* 2002;22(24):10819–10828
25. Gottfried JA, O'Doherty J, Dolan RJ. Encoding predictive reward value in human amygdala and orbitofrontal cortex. *Science* 2003;301(5636):1104–1107
26. Doty RL. Office procedures for quantitative assessment of olfactory function. *Am J Rhinol* 2007;21(4):460–473
27. Kobal G. Electrophysiological measurement of olfactory function. In: Doty RL, ed. *Handbook of Olfaction and Gustation*. 2nd ed. New York: Marcel Dekker; 2003:229–249
28. Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function. *Physiol Behav* 1984;32:489–502
29. Doty RL, Laing DG. Psychophysical measurement of olfactory function, including odorant mixture assessment. In: Doty RL, ed. *Handbook of Olfaction and Gustation*. 2nd ed. New York: Marcel Dekker; 2003:203–228
30. Betchen SA, Doty RL. Bilateral detection thresholds in dextrals and sinistrals reflect the more sensitive side of the nose, which is not lateralized. *Chem Senses* 1998;23:453–457
31. Murphy C, Doty RL, Duncan HJ. Clinical disorders of olfaction. In: Doty RL, ed. *Handbook of Olfaction and Gustation*. 2nd ed. New York: Marcel Dekker; 2003:461–478
32. Krmpotić-Nemanić J. Presbycusis, presbystasis and presbyosmia as consequences of the analogous biological process. *Acta Otolaryngol* 1969;67(2):217–223
33. Kalmey JK, Thewissen JG, Dluzen DE. Age-related size reduction of foramina in the cribriform plate. *Anat Rec* 1998;251(3):326–329
34. Doty RL, Shaman P, Applebaum SL, Giberson R, Siksorski L, Rosenberg L. Smell identification ability: changes with age. *Science* 1984;226:1441–1443
35. Doty RL. Olfaction and gustation in normal aging and Alzheimer's disease. In: Hoff PR, Mobbs CV, eds. *Functional Neurobiology of Aging*. San Diego: Academic Press; 2001:647–658
36. Breipohl W, Mackay-Sim A, Grandt D, Rehn B, Darrelmann C. Neurogenesis in the vertebrate main olfactory epithelium. In: Breipohl W, ed. *Ontogeny of Olfaction*. Berlin: Springer-Verlag; 1986:21–33
37. Stroop WG. Viruses and the olfactory system. In: Doty RL, ed. *Handbook of Olfaction and Gustation*. New York: Marcel Dekker; 1995:367–393
38. Baker H, Genter MB. The olfactory system and the nasal mucosa as portals of entry of viruses, drugs, and other exogenous agents into the brain. In: Doty RL, ed. *Handbook of Olfaction and Gustation*. New York: Marcel Dekker; 2003:549–573
39. Brownstein DG. Resistance/susceptibility to lethal Sendai virus infection genetically linked to a mucociliary transport polymorphism. *J Virol* 1987;61(5):1670–1671
40. Fiser DJ, Borotski L. Anosmia after administration of influenza vaccine. *Med Pregl* 1979;32:455–457
41. Zaidel DW, Hugdahl K, Johnsen BH. Physiological responses to verbally inaccessible pictorial information in the left and right hemispheres. *Neuropsychology* 1995;9(1):52–57
42. Doty RL, Hastings L. Neurotoxic exposure and olfactory impairment. *Clin Occupat Environ Med* 2001;1:547–575
43. Gottofrey J, Tjalve H. Axonal transport of cadmium in the olfactory nerve of the pike. *Pharmacol Toxicol* 1991;69(4):242–252
44. Tjalve H, Henriksson J, Tallkvist J, Larsson BS, Lindquist NG. Uptake of manganese and cadmium from the nasal mucosa into the central nervous system via olfactory pathways in rats. *Pharmacol Toxicol* 1996;79(6):347–356
45. Tjalve H, Henriksson J. Uptake of metals in the brain via olfactory pathways. *Neurotoxicology* 1999;20(2–3):181–195
46. Santorelli G, Marotta A. [Olfactometric threshold of the epileptic in basal conditions and after crises: experimental

- confirmation of data registered in the clinic]. *Osp Psichiatri* 1964;32:185–190
47. Abraham A, Mathai KV. The effect of right temporal lobe lesions on matching of smells. *Neuropsychologia* 1983;21(3):277–281
 48. Carroll B, Richardson JT, Thompson P. Olfactory information processing and temporal lobe epilepsy. *Brain Cogn* 1993;22(2):230–243
 49. Kohler CG, Moberg PJ, Gur RE, O'Connor MJ, Sperling MR, Doty RL. Olfactory dysfunction in schizophrenia and temporal lobe epilepsy. *Neuropsychiatry Neuropsychol Behav Neurol* 2001;14(2):83–88
 50. Martinez BA, Cain WS, de Wijk RA, Spencer DD, Novelty RA, Sass KJ. Olfactory functioning before and after temporal lobe resection for intractable seizures. *Neuropsychology* 1993;7(3):351–363
 51. Hummel T, Pauli E, Schuler P, Kettenmann B, Stefan H, Kobal G. Chemosensory event-related potentials in patients with temporal lobe epilepsy. *Epilepsia* 1995;36(1):79–85
 52. Doty RL, Stern MB, Pfeiffer C, Gollomp SM, Hurtig HI. Bilateral olfactory dysfunction in early stage treated and untreated idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1992;55(2):138–142
 53. Quinn NP, Rossor MN, Marsden CD. Olfactory threshold in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1987;50:88–89
 54. Roth J, Radil T, Ruzicka E, Jech R, Tichy J. Apomorphine does not influence olfactory thresholds in Parkinson's disease. *Funct Neurol* 1998;13(2):99–103
 55. Doty RL, Riklan M, Deems DA, Reynolds C, Stellar S. The olfactory and cognitive deficits of Parkinson's disease: evidence for independence. *Ann Neurol* 1989;25(2):166–171
 56. Doty RL, Bromley SM, Stern MB. Olfactory testing as an aid in the diagnosis of Parkinson's disease: development of optimal discrimination criteria. *Neurodegeneration* 1995;4(1):93–97
 57. Ponsen MM, Stoffers D, Booi J, van Eck-Smit BL, Wolters EC, Berendse HW. Idiopathic hyposmia as a preclinical sign of Parkinson's disease. *Ann Neurol* 2004;56(2):173–181
 58. Braak H, Rub U, Del Tredici K. Cognitive decline correlates with neuropathological stage in Parkinson's disease. *J Neurol Sci* 2006;248(1–2):255–258
 59. Hawkes CH, Del Tredici K, Braak H. Parkinson's disease: a dual hit hypothesis. *Mov Disord* 2007;22:S248
 60. Sajjadian A, Doty RL, Gutnick DN, Chirugi RJ, Sivak M, Perl D. Olfactory dysfunction in amyotrophic lateral sclerosis. *Neurodegeneration* 1994;3:153–157
 61. Moberg PJ, Doty RL, Turetsky BI, et al. Olfactory identification deficits in schizophrenia: correlation with duration of illness. *Am J Psychiatry* 1997;154(7):1016–1018
 62. Moberg PJ, Doty RL. Olfactory function in Huntington's disease patients and at-risk offspring. *Int J Neurosci* 1997;89(1–2):133–139
 63. Wenning GK, Shephard B, Hawkes C, Petrukevitch A, Lees A, Quinn N. Olfactory function in atypical parkinsonian syndromes. *Acta Neurol Scand* 1995;91(4):247–250
 64. Doty RL, Singh A, Tetrad J, Langston JW. Lack of major olfactory dysfunction in MPTP-induced parkinsonism. *Ann Neurol* 1992;32(1):97–100
 65. Doty RL, Golbe LI, McKeown DA, Stern MB, Lehrach CM, Crawford D. Olfactory testing differentiates between progressive supranuclear palsy and idiopathic Parkinson's disease. *Neurology* 1993;43(5):962–965
 66. Montgomery EB Jr, Koller WC, LaMantia TJ, et al. Early detection of probable idiopathic Parkinson's disease: I. Development of a diagnostic test battery. *Mov Disord* 2000;15(3):467–473
 67. Hawkes CH, Shephard BC, Daniel SE. Is Parkinson's disease a primary olfactory disorder? *QJM* 1999;92(8):473–480
 68. Markopoulou K, Larsen KW, Wszolek EK, et al. Olfactory dysfunction in familial parkinsonism. *Neurology* 1997;49(5):1262–1267
 69. Hentschel K, Furtado S, Markopoulou K, Doty RL, Uitti RJ, Wszolek ZK. Differences in olfactory dysfunction between sporadic PD and familial Parkinson's disease kindreds by UPSIT subgroup analysis. *Mov Disord* 2005;20:S55
 70. Chen MA, Lander TR, Murphy C. Nasal health in Down syndrome: a cross-sectional study. *Otolaryngol Head Neck Surg* 2006;134(5):741–745
 71. McKeown DA, Doty RL, Perl DP, Frye RE, Simms I. Mester. Olfactory function in young adolescents with Down's syndrome. *J Neurol Neurosurg Psychiatry* 1996;61(4):412–414
 72. Bylsma FW, Moberg PJ, Doty RL, Brandt J. Odor identification in Huntington's disease patients and asymptomatic gene carriers. *J Neuropsychiatry Clin Neurosci* 1997;9(4):598–600
 73. Doty RL, Li C, Mannon LJ, Yousem DM. Olfactory dysfunction in multiple sclerosis. *N Engl J Med* 1997;336(26):1918–1919
 74. Doty RL, Li C, Mannon LJ, Yousem DM. Olfactory dysfunction in multiple sclerosis: relation to longitudinal changes in plaque numbers in central olfactory structures. *Neurology* 1999;53(4):880–882
 75. Tabaton M, Monaco S, Cordone MP, et al. Prion deposition in olfactory biopsy of sporadic Creutzfeldt-Jakob disease. *Ann Neurol* 2004;55(2):294–296
 76. Zanusso G, Ferrari S, Cardone F, et al. Detection of pathologic prion protein in the olfactory epithelium in sporadic Creutzfeldt-Jakob disease. *N Engl J Med* 2003;348(8):711–719
 77. Doty RL, Yousem DM, Pham LT, Kreshak AA, Geckle R, Lee WW. Olfactory dysfunction in patients with head trauma. *Arch Neurol* 1997;54(9):1131–1140
 78. London B, Nabet B, Fisher AR, White B, Sammel MD, Doty RL. Predictors of prognosis in patients with olfactory disturbance. *Ann Neurol* 2008;63(2):159–166
 79. Hirsch AR. Olfaction in migraineurs. *Headache* 1992;32(5):233–236
 80. Yousem DM, Geckle RJ, Bilker WB, McKeown DA, Doty RL. Posttraumatic olfactory dysfunction: MR and clinical evaluation. *AJNR Am J Neuroradiol* 1996;17(6):1171–1179
 81. Schwob JE, Szumowski KE, Leopold DA, Emko P. Histopathology of olfactory mucosa in Kallmann's syndrome. *Ann Otol Rhinol Laryngol* 1993;102(2):117–122