OLFACTION

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Abstract The main and accessory olfactory systems have received considerable attention on the part of scientists and clinicians during the last decade, largely because of (a) quantum advances in understanding their genetically expressed receptor mechanisms, (b) evidence that their receptor cells undergo neurogenesis and both programmed and induced cell death, and (c) important technical and practical developments in psychophysical measurement. The latter developments have led to the proliferation of standardized olfactory testing in laboratories and clinics, and to the discovery that smell loss is among the first signs of a number of neurodegenerative diseases, including Alzheimer's disease and idiopathic Parkinson's disease. Recent controversial claims that humans possess a functioning vomeronasal system responsive to "pheromones" has added further interest in intranasal chemoreception. This review focuses on recent progress made in understanding olfactory function, emphasizing transduction, measurement, and clinical findings.

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INTRODUCTION

Most land mammals possess, within their left and right nasal chambers, receptors or elements of five specialized neural systems: (a) the main olfactory system (cranial nerve I or CN I), (b) the vomeronasal or accessory olfactory system, (c) the trigeminal somatosensory system (CN V), (d) the septal organ of Masera, and (e) the nervus terminalis or terminal nerve (CN 0). CN I mediates what we commonly term odor sensations (e.g. rose, chocolate, strawberry, apple, etc) and is responsible, in large part, for the flavor of foods and beverages, as well as numerous other chemically mediated aesthetic perceptions. Additionally, this system serves as an early warning system for spoiled food and noxious or dangerous environmental chemicals. CN V mediates, via both chemical and nonchemical stimuli, somatosensory sensations (e.g. irritation, burning, cooling, and tickling), and induces reflexive responses, such as secretion of mucus and halting of inhalation, that prevent or minimize chemically or thermally induced injury to the nasal and pulmonary passages. The nature of vomeronasal and CN 0 sensations, if any, are unknown to humans, whereas those of the septal organ—a small patch of neuroepithelial tissue on the anterior ventral nasal septum—are presumably the sensations of CN I in those species that possess this structure. The latter organ, whose histology is similar to that of the main olfactory epithelium, sends its axons to a relatively circumscribed region of the main olfactory bulb (Astic & Saucier 1988) and is electrophysiologically responsive, at least in the rat, to the same sets of stimuli as CN I (Marshall & Maruniak 1986). Although this organ has been well described in rodents, lagomorphs, and marsupials (e.g. the bandicoot, house mouse, deer mouse, Norway rat, hamster, rabbit, and guinea pig), its existence in other mammals has not been established.

CN 0 was discovered after the other cranial nerves had been named and is highly conserved, with remarkably constant anatomy across all vertebrate species, including humans (Schwanzel-Fukuda & Pfaff 1995). Its peripheral component is a loose plexus distinguished by the presence of ganglia at nodal points. This nerve, notable for its high gonadotropin-releasing hormone (GnRH) content, ramifies throughout the nasal epithelium before crossing the nasal mucosa and coursing through the foramina of the cribriform plate medial to the olfactory nerves. In rodents, it converges centrally into three or four rootlets that enter the forebrain caudal to the medial sides of the olfactory bulbs (Schwanzel-Fukuda & Pfaff 1995). It has been suggested that CN 0 may help modulate the vascular pump that brings stimuli into the accessory olfactory system’s vomeronasal organ (VNO), an elongated tubelike structure located at the base of the nasal septum (Wirsig-Wiechmann & Lepri 1991). However, it is consistently present in animals lacking functional main and accessory olfactory systems, such as porpoises (Schwanzel-Fukuda & Pfaff 1995). Despite the possibility that CN 0 may play a sensory role in some species (Demski 1993), evidence for a chemosensory role is generally lacking. An endocrine role is supported by the fact that deficits in mating behavior occur in male hamsters after its central rootlets are severed, whereas tactile-induced
lordosis in female hamsters is facilitated after such lesions (Wirsig-Wiechmann 1997). The GnRH content of the nervus terminalis is regulated, at least in part, by estrogen (Wirsig-Wiechmann & Lee 1999).

This review focuses on the primary and accessory olfactory systems because these are the most salient and widely studied nasal chemosensory systems of vertebrates. These systems employ different projection pathways to different regions of the amygdala and hypothalamus (Scalia & Winans 1975). Advances in practical psychophysical measurement of CN I and attendant findings in humans are presented, along with advances in functional imaging techniques destined to increase our understanding of central olfactory coding. The question of whether humans possess a functioning vomeronasal organ is addressed, and recent studies that further elucidate the function of the vomeronasal organ in nonhuman forms are described.

THE MAIN OLFACTORY SYSTEM (CN I)

General Anatomy

In humans, the sensory receptors of the main olfactory system are located in the upper recesses of the nasal chambers within a neuroepithelium lining the cribriform plate and sectors of the superior turbinate, middle turbinate, and septum. In amphibia, the neuroepithelium is flat and planar, whereas in rodents, carnivores, and many other mammals, it is distributed over a very convoluted surface dictated by the complexity of the turbinal folds arising from the ethmoid bone. The number of ethmoidal turbinates varies among species, extending from one to three in primates to over a dozen in the spiny anteater (Echidna). Although only a single row of turbinates—termed ectoturbinates—is found in primates, in many other forms, including most rodent and carnivores, two rows of turbinates are present, the more central row being termed endoturbinates (Negus 1958).

The olfactory epithelium is comprised of at least six morphologically and biochemically distinct cell types (Huard et al 1998), although additional classes of less well-defined microvilli-containing cells have been noted prenatally (Menco & Jackson 1997b) and postnatally (Carr et al 1991). The first cell type—the bipolar sensory receptor neuron—extends odorant receptor–containing cilia into the mucus. The axons of these cells, in aggregate, constitute CN I. In most vertebrates, including humans, the number of receptor cells exceeds that of any other sensory system except vision. Collectively, the surface area of the cilia is quite large, being estimated as exceeding, for example, 22 cm² in the human (Doty 1998) and 7 m² (not cm!) in the German shepherd dog (Moulton 1977). The second cell type is the supporting or sustentacular cell. These cells, which have microvilli rather than cilia, insulate the bipolar receptor cells from one another and may help regulate the composition of the mucus. They also likely deactivate odorants, as well as help to protect the epithelium from damage from foreign agents. The supporting
cells contain xenobiotic-metabolizing enzymes (e.g. cytochrome P-450), a feature shared with the acinar and duct cells of Bowman’s glands, the major source of mucus in the olfactory epithelium. The third cell type is the poorly understood microvillar cell located at the surface of the epithelium. Microvillar cells, which look similar to the so-called brush cells found throughout the upper and lower airways of many species, extend axon-like processes to the olfactory bulb and, like the supporting cells, have microvilli at their apical surfaces. In the human, microvillar cells occur in about a 1:10 ratio with the bipolar receptor cells. A chemosensory function of these cells has yet to be demonstrated, and preliminary in vitro patch clamp studies of dissociated microvillar cells have failed to find them responsive to odorants (N Rawson, personal communication). The fourth cell type is the cell that lines the Bowman’s glands and ducts, whereas the fifth and sixth cell types are the globose (light) basal cell and horizontal (dark) basal cell—cells located near the basement membrane from which most of the other cell types arise. Recent data suggest that, under conditions of marked damage to the olfactory epithelium, the same type of basal cell, most likely a globose cell, seems to have the potential for giving rise to neurons and nonneural cells, including the horizontal basal cells, implying a multipotency in stem cells not previously recognized (Huard et al 1998).

The cilia of the bipolar receptor cells, which differ from the cilia of the cells making up the respiratory epithelium in being much longer and lacking dynein arms (hence, intrinsic motility), contain the seven domain transmembrane receptors that interact with incoming odorants. In some cases, the transport of odorants through the mucus to the cilia is aided by transporting molecules termed odorant binding proteins. In situ hybridization studies with probes to putative odor receptors of rats and mice suggest the receptors are topographically organized, in these species, into four striplike zones within the olfactory epithelium that roughly parallel the dorsal-ventral axis of the cribriform plate (Vassar et al 1993). Approximately 1000 putative odorant receptors are believed to exist, reflecting the expression of the largest known vertebrate gene family—a gene family that accounts for ~1% of all expressed genes (Buck & Axel 1991). In general, putative receptors of a given type are confined to one of the four zones. Menco & Jackson (1997a), employing scanning electron microscopy, have recently shown a possible morphological correlate to these zones—by embryonic day 16, the posterior regions (roughly corresponding to zones 1 and 2) have much higher receptor cell knob densities than the more anterior regions (corresponding to zones 3 and 4). Furthermore, the supporting cell microvilli are longer in region 1 than in region 2, and the tops of cells adjacent to the receptor cells are flatter in regions 1 and 2 than in regions 3 and 4. Regions 3 and 4 also have glandular openings and scattered microvillous cells that resemble hair cells of the inner ear.

In the human, the axons of the ~6 million bipolar receptor cells coalesce into 30–40 fascicles, termed the olfactory fila, which are formed by ensheathing glia. The
fila traverse the cribriform plate and pia matter, and the axons make connections within the olfactory bulb. It is now believed that the neurotransmitter of the receptor cells is glutamate (Trombley & Shepherd 1993), although the olfactory bulb itself contains a remarkable number of neurotransmitters. In situ hybridization studies have shown that, in the rat and mouse, neurons expressing a given receptor type typically project their axons to one or, at most, two glomeruli—spherical structures within the outer margins of the olfactory bulb (Mombaerts et al 1996). This implies that a given odorant activates a spatially defined or restricted set of glomeruli and that the olfactory code is reflected, at this early stage, not only as different patterns across the mucosa (Kent et al 1995), but across the glomeruli as well (Vassar et al 1994).

The axons of the major second-order neurons—the mitral and tufted cells—come under considerable modulation via inhibitory processes within the bulb, resulting in the sharpening or altering of the neural information at this level. The mitral and tufted cells project directly to the primary olfactory cortex without synapsing with the thalamus. Although commonly divided into “lateral” and “medial” olfactory tracts in textbooks of anatomy, there is no medial tract in primates (Price 1990). The olfactory cortex is comprised of (a) the anterior olfactory nucleus, (b) the prepiriform cortex, (c) the lateral entorhinal cortex, (d) the periamygdaloid cortex (a region contiguous with the underlying amygdala), and (e) the cortical nucleus of the amygdala. Major connections between the primary olfactory cortex and the secondary olfactory cortex in the orbitofrontal region occur via the mediodorsal nucleus of the thalamus, as well as via direct cortico-cortical projections from prorhinal cortex to the posterolateral orbitofrontal region.

Transduction Mechanisms

During the past decade there have been monumental strides in understanding the initial events of olfactory transduction, beginning with the identification of a large gene family that likely encodes olfactory receptors (Buck & Axel 1991). Although a given receptor cell seems to express only one type of receptor derived from a single allele (Chess et al 1994), each cell is electrophysiologically responsive to a wide, but circumscribed, range of stimuli (Holley et al 1974). This implies that a single receptor accepts a range of molecular entities, and that coding occurs via a complex cross-fiber patterning of responses. Odorant binding leads to an inwardly depolarizing current within the cilia of the bipolar receptor cells that ultimately triggers the action potentials that collectively provide the neural code that is deciphered by higher brain centers.

Most, if not all, of the olfactory receptor proteins are linked to the stimulatory guanine nucleotide-binding protein $G_{olf}$ (Jones & Reed 1989). When stimulated, they activate the enzyme adenylate cyclase to produce the second messenger adenosine monophosphate (cAMP) (Lowe et al 1989). $G_{olf}$-induced cAMP
diffuses through the cell and activates cellular depolarization via the opening of cyclic-nucleotide-gated ionic channels and Ca$^{2+}$-dependent Cl$^-$ or K$^+$ channels (Restrepo et al 1993, Firestein et al 1991). The amount of adenylate cyclase activity produced by various odorants in a frog ciliary preparation (Sklar et al 1986) is positively correlated with the magnitude of the frog's electro-olfactogram (a surface potential associated with the number of receptors activated; Lowe et al 1989), as well as with the perceived intensity of these same odorants to humans (Doty et al 1990). Some odorants also activate cyclic guanosine monophosphate (cGMP), which is believed to play a role in the modulation of the sensitivity of olfactory receptor neurons, such as during adaptation (Leinders-Zufall et al 1996).

Although G proteins other than G$\text{olf}$ (e.g. G$\text{i2}$ and G$\text{o}$) have been identified in olfactory receptor cells, they appear not to be involved in early transduction events, likely assisting in such processes as axonal signal propagation, axon sorting, and target innervation (Wekesa & Anholt 1999).

Prior to the discovery of G$\text{olf}$, support for the hypothesis that another G protein, G$\text{s}$, plays a major role in the initial phases of olfactory transduction in humans came from findings of variably decreased olfactory ability in type Ia pseudohypoparathyroidism (PHP). PHP is a syndrome in which generalized hormone resistance is associated with a deficiency of G$\text{s}$, as measured in red blood cells (Weinstock et al 1986). However, these patients have other problems that might cause or contribute to their olfactory dysfunction, including an unusual constellation of skeletal and developmental deficits termed Albright hereditary osteodystrophy (AHO). Whereas a more recent study has confirmed that PHP type Ia patients have defective olfaction, patients with type Ib PHP, who have no AHO, no generalized hormone resistance, and normal G$\text{s}$ activity, also exhibited olfactory dysfunction relative to matched controls (Doty et al 1997a). Furthermore, patients with pseudopseudohypoparathyroidism, who have AHO, no generalized hormone resistance, and deficient G$\text{s}$ protein activity, were found to have relatively normal olfactory function. These observations do not support the hypothesis that the olfactory dysfunction associated with PHP is the result of generalized G$\text{s}$ protein deficiency and imply that other mechanisms are responsible for the olfactory deficits of this disorder. Whether G$\text{olf}$ is deficient in the olfactory epithelia of PHP patients has not been determined.

Although it is generally thought that some odorants activate a second transduction pathway in vertebrates (namely, that associated with the activation of the enzyme phospholipase C to produce the second messenger inositol triphosphate or IP$_3$) (Breer & Boekhoff 1991), recent data suggest this may not be the case, at least in mice (Gold 1999). The discordant studies have employed knockout mice in which genes responsible for both the cyclic-nucleotide-gated ion channel and for G$\text{olf}$ have been deleted. In the channel knockout mouse, electro-olfactogram responses to all odors tested were eliminated, including those previously believed to be mediated by the IP$_3$ system (Brunet et al 1996). To date, IP$_3$-gated channels have not been demonstrated in mammalian olfactory nerve cells using patch clamp techniques (Firestein et al 1991, Lowe & Gold 1993).
A significant development in understanding the nature of olfactory transduction is the functional characterization of odorant receptors themselves. Several approaches have been employed. Zhao et al (1998) used an adenovirus-mediated gene transfer procedure to increase the expression of a specific receptor gene in an increased number of receptor neurons in the rat olfactory epithelium, demonstrating ligand-specific increases in electro-olfactogram amplitude. Krautwurst et al (1998) employed a polymerase chain reaction strategy to generate an olfactory receptor library from which cloned receptors were screened for odorant-induced responsiveness to a panel of odorants, as measured by an assay sensitive to intracellular Ca\(^{2+}\) changes. Several receptor types with ligand specificity were found, including one differentially sensitive to the (-) and (+) stereoisomers of citronella.

**Olfactory Receptor Cell Regeneration**

An important ongoing revolution in the field of olfaction is the elucidation of the nature of degeneration and regeneration within the olfactory neuroepithelium. Unlike the sensory neurons of other major systems, those of the olfactory epithelium have a propensity to replace themselves after injury. Although it was long thought—largely on the basis of \(^{3}\text{H}\)thymidine studies—that the olfactory neuroepithelium undergoes complete cell turnover every 30 or so days (Graziadei & Monti Graziadei 1979), recent data suggest that the situation is much more complex. Thus, many receptor cells are relatively long-lived despite continuous neurogenesis within the olfactory epithelium (Hinds et al 1984), and both endogenous and exogenous factors promote receptor cell death or replenishment from progenitor stem cells (Mackay-Sim & Kittel 1990). Interestingly, the receptor cells of older animals appear to live longer than those of younger animals (Weiler & Farbman 1999b).

Biochemical or mechanical stress appears to induce subgroups of stem cells to differentiate into mature olfactory receptor cells (Feron et al 1999), and differentiated neurons send back regulatory signals that inform the neuronal progenitor cells as to the numbers of new neurons that need to be produced to maintain equilibrium in the cell population (Calof et al 1998b). Importantly, apoptotic cell death has been observed in cells representing all stages of regeneration (e.g. in proliferating neuronal precursors, immature olfactory receptor neurons, and mature olfactory receptor neurons), implying that apoptotic regulation of neuronal numbers may occur at multiple stages of the neuronal lineage (Holcomb et al 1995). Recently, it has been shown that the mitral cells of the bulb may contain a trophic substance that helps to maintain the survival of olfactory receptor neurons (Weiler & Farbman 1999a). Chemical factors that inhibit (e.g. fibroblast growth factor-2, bone morphogenetic proteins, dopamine) or promote (e.g. transforming growth factor-alpha, olfactory marker protein) neurogenesis or differentiation, or actively produce apoptotic cascades (e.g. tumor necrosis factor-alpha, Fas ligand), are currently under active investigation (Calof et al 1998a, Goldstein et al 1997, Shou et al 1999, Farbman et al 1999, MacDonald et al 1996).
It is noteworthy that the olfactory ensheathing cells, which form the bundles of axons that make up the fila containing the olfactory receptor cell axons that traverse the cribriform plate and constitute the outermost layer of the olfactory bulb, have been found to have unique properties useful in repair or regeneration of both central and peripheral nerves. They exhibit, for example, both Schwann cell- and astrocyte-like properties, and have been shown to enhance remyelination and axonal conduction in demyelinated spinal tract nerves, as well as in the joining of severed rat sciatic nerves (Verdú et al 1999, Imaizumi et al 1998).

**Functional Imaging Studies of the Human Olfactory System**

The advent of functional imaging procedures such as positron emission tomography, single photon emission computed tomography, and functional magnetic resonance imaging (fMRI) now makes it possible to establish, in vivo, brain regions activated by odors, as well as by the act of sniffing. Although the spatial resolution of these imaging techniques limits the degree to which activity in some structures can be visualized (e.g. the olfactory bulbs), odor-induced activation of most of the major olfactory-related cortical structures has been observed, albeit in some cases sporadically. This includes the piriform cortex, the orbitofrontal cortex, and the inferior frontal lobe (Koizuka et al 1994, Zatorre et al 1992, Dade et al 1998, Yousem et al 1997). Recently, Sobel et al (2000) demonstrated that inconsistent activation of primary olfactory cortex in fMRI studies likely reflects sampling factors and the time course of activation in these regions. Their data, along with those from animal studies, suggest that rapid habituation occurs in the primary olfactory cortex despite continued odorant presentation and detection. By employing statistical procedures sensitive to temporal changes in signal variability and magnitude, these authors have demonstrated that consistent fMRI-related activation of primary olfactory cortex structures can be obtained.

fMRI studies demonstrating decreased relative activation with age and less activation in men than in women are in accord with psychophysical findings (Yousem et al 1999b,c). Interestingly, an early positron emission tomography study found that the right orbitofrontal cortex was more activated by odorants than the contralateral homologous orbitalfrontal cortex, whereas the medial temporal lobes were symmetrically activated (Zatorre et al 1992). This suggested the hypothesis that some right hemisphere structures may be more specialized than corresponding structures in the left hemisphere in encoding olfactory information. Greater right-than left-side activation has been observed in subsequent studies, including those employing single photon emission computed tomography (Malaspina et al 1998) and fMRI (Yousem et al 1997, Terashima 1988), although reports of greater left than right activation for aversive stimuli, as well as equal activation for other stimuli, have also appeared (Koizuka et al 1994, Zald & Pardo 1997). Interestingly, psychophysical findings of better right than left performance on tests of odor discrimination and memory (but not detection-threshold sensitivity) have also been reported (Zatorre & Jones-Gotman 1991; RL Dotv. unpublished).
Recently, Royet et al (2000) performed a positron emission tomography study to establish whether different odor-related cognitive tasks activated different central olfactory structures. Regional cerebral blood flow was determined in 15 normal participants under 3 yes/no conditions in which they reported whether an odor was (a) present (control detection task), (b) familiar, or (c) edible. The authors hypothesized that the detection task required a superficial judgment that did not involve stored representations of odors, whereas the other two tasks, respectively, required the activation of perceptual and perceptual plus semantic neural representations of odors. Thus, a hierarchy of complexity (and thus breadth of activation) was hypothesized: detection task > familiarity task > edibility task. In some analyses, the detection task activation was subtracted from the activation of the other two conditions, whereas in one the familiarity task activation was subtracted from that of the edibility task. These subtractions were done to better define the unique activation of each of the two presumed higher-order conditions. Although their general hierarchy theory was not supported, these investigators found that the familiarity judgments were mainly associated with increased regional cerebral blood flow in the right orbitofrontal area, the subcallosal gyrus, the left inferior and superior frontal gyri, and the anterior cingulate cortices. Edibility judgments selectively activated the primary visual areas, suggesting that visual imagery was evoked by this task. In contrast, decreased regional cerebral blood flow occurred in the visual regions under the familiarity judgment task, and in the orbitofrontal regions under the edibility task. This pioneering study suggests that orbital regions are involved in judgments of odor quality, and that orbitofrontal and visual cortices may interact with one another in some types of odor-related tasks.

An intriguing discovery from several functional imaging studies is that odors reliably and significantly activate regions of the human cerebellum, a structure classically considered to be involved mainly in motor learning (Sobel et al 1998a,b; Yousem et al 1997). Whereas there are early clinical reports of olfactory dysfunction in patients with tumors near the cerebellum (Tucker 1911, Peregud 1931), the cerebellar activity was unexpected and serendipitous in light of current knowledge of the olfactory projection pathways and views of the cerebellum. Interestingly, other functional imaging studies have now implicated the cerebellum in a broad range of sensory and cognitive processing tasks (Kim et al 1994, Gao et al 1996, Hanamori et al 1986). In a detailed assessment of the influences of odor on fMRI-determined cerebellar activity, Sobel et al (1998b) found that odorants activated, in a concentration-dependent manner, largely posterior lateral areas of the cerebellum. On the other hand, sniffing blank air activated mainly anterior central cerebellar regions. Generalizing a model proposed by Bower et al (1981) to explain tactile activation of the cerebellum, Sobel et al (1998b, p. 8998) suggested the hypothesis that “the cerebellum is monitoring incoming data (odorant concentration) and adjusting the position of the stimulus (odorant air stream) relative to the sensory surface (olfactory epithelium) by controlling the motor behavior (sniff), in real time.”
Development of Standardized Psychophysical Tests of Human Olfactory Function

Advances in the technology of psychophysical measurement and the proliferation of easy-to-use tests of olfactory function have significantly increased our understanding of the sense of smell in humans, including the functional influences of such factors as age, gender, exposure to toxic agents, and various disease states. During the past decade, standardized and practical psychophysical tests have become widely employed, with several becoming commercially available. Such tests include the 40-odor University of Pennsylvania Smell Identification Test (UPSIT; known commercially as the Smell Identification Test™ or SIT) (Doty et al 1984b, Doty 1995), the 12-odor Brief-Smell Identification Test™ (also known as the Cross-Cultural Smell Identification Test™) (Doty et al 1996), the 3-odor Pocket Smell Test™ (Doty et al 1995), the 12-item Odor Memory Test™ (Doty et al 1995b, Bromley & Doty 1995b), the Odor Confusion Matrix Test (Wright 1987), the San Diego Odor Identification Test (Anderson et al 1992), the Scandinavian Odor Identification Test (Nordin et al 1999), the “Sniff ‘n Sticks” test (Hummel et al 1997), the Viennese Olfactory Test Battery (Lehrner & Deecke 1999), an 8-odor identification test (Simmen et al 1999), and several tests of odor threshold, including the T&T olfactometer test (Takagi 1989) and the Smell Threshold Test™ (Doty 2000).

Of these tests, the UPSIT has proved to be the most popular, having been administered to ~180,000 people in Europe and North America. This highly reliable (test-retest r = 0.94) (Doty et al 1989), self-administered microencapsulated odor-ant test employs norms based upon nearly 4000 persons, and is available in English, Spanish, French, and German versions (Doty et al 1984b, Doty 1995). The UPSIT was the impetus for a massive smell function survey sent to nearly 11 million subscribers of National Geographic in 1986 (Gibbons 1986, Gilbert & Wysocki 1987).

Application of Standardized Psychophysical Tests to Normal and Clinical Populations

Major nonclinical findings of the past decade and a half that have been derived from such tests, primarily the UPSIT, include the following: (a) women, on average, have a better sense of smell than men—superiority that spans cultures and is noticable as early as four years of age (Doty 1986; Doty et al 1984a, 1985; Liu et al 1995); (b) there is a substantial genetic influence on the ability of humans to identify odors (Segal et al 1992, 1995); (c) major loss of olfactory function occurs after age 65, with over half of those between 65 and 80, and over three quarters of those 80 years of age and older, having such loss (Doty et al 1984a, Ship & Weiffenbach 1993, Liu et al 1995); (d) women, on average, retain the ability to smell longer than men (Doty et al 1984a); (e) the decrement in olfactory function associated with smoking is present in former smokers and recovery to presmoking levels, while possible, can take years, depending upon the duration and amount...
of past smoking (Frye et al 1990); and (e) olfactory function is compromised in urban residents and workers in some industries, including the paper and chemical manufacturing industries (Schwartz et al 1989, 1990, 1991; Ahman et al 1996; Hirsch & Zavala 1999).

Clinical studies employing such methodology during this period have found—to one degree or another—decreased smell function, relative to matched controls, in a wide variety of diseases and conditions, as listed in Table 1. It is noteworthy that such tests have also found that a number of disorders are not associated with meaningful smell losses, including corticobasal degeneration (Wenning et al 1995), depression (Amsterdam et al 1987), panic disorder (Kopala & Good 1996), progressive supranuclear palsy (Wenning et al 1995, Doty et al 1993), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism (Doty et al 1992a), essential tremor (Busenbark 1991), and multiple chemical hypersensitivity (Doty et al 1988a). Such findings suggest that smell dysfunction can aid in differential diagnosis among several neurodegenerative disorders, especially those that present with clinical signs similar to those of Alzheimer’s disease, Parkinson’s disease, and schizophrenia. McCaffrey et al (2000) have recently shown that even the 3-item Pocket Smell Test TM discriminates better between patients with Alzheimer’s disease and major affective disorder (i.e. depression) than the widely used 30-item Mini-Mental State Examination.

The ability to quantify olfactory function using the aforementioned tests, along with advances in in vivo medical imaging, has allowed for a better understanding of the underlying reasons for olfactory loss in some patients. We now know, for example, that congenitally anosmic individuals typically lack, or have markedly deformed, olfactory bulbs and stalks, as determined from MRI studies (Yousem et al 1996a). Furthermore, patients who have head trauma–related smell loss typically exhibit contusions of the frontal and temporal poles of the brain, as well as a decrease in the size of their olfactory bulbs and tracts (Doty et al 1997c, Yousem et al 1996b). The latter finding may reflect mitigation of trophic factors from the olfactory receptor neurons, which are often sheared off or otherwise damaged in head trauma cases. The olfactory dysfunction associated with chronic alcoholism has been found to be correlated with MRI-determined (a) increased cortical and ventricular cerebral spinal fluid volumes and (b) reduced volumes of the thalamus and of cortical and subcortical gray matter (Shear et al 1992). In multiple sclerosis, a strong inverse correlation ($r = -0.94$) has been observed between UPSIT scores and the number of MRI-determined plaques within central brain structures associated with olfactory processing (inferior frontal and temporal lobes)—a correlation not present when plaque numbers in other brain regions were similarly examined (Doty et al 1997b, 1998). A 1:1 association was recently observed, longitudinally, between UPSIT scores and the remission and exacerbation of such plaque numbers in each of 5 multiple sclerosis patients tested over an 18- to 20-month period, with greater numbers of plaques reflecting lower UPSIT scores (Doty et al 1999). Hence, discrepant findings among studies evaluating olfactory function in multiple sclerosis patients likely reflects the waxing and waning, over time, of plaques in central olfactory structures.
**TABLE 1** Examples of medical conditions or disorders associated with olfactory dysfunction, as measured by modern quantitative tests of olfactory function, particularly the UPSIT

<table>
<thead>
<tr>
<th>Medical condition</th>
<th>References</th>
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<tbody>
<tr>
<td>Attention deficit/hyperactivity disorders</td>
<td>Gansler et al 1998</td>
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<tr>
<td>Anorexia nervosa—severe stage</td>
<td>Fedoroff et al 1995</td>
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<tr>
<td>Breast cancer-estrogen receptor positive</td>
<td>Lehrer et al 1985</td>
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<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>Dewan et al 1990</td>
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<td>Cystic fibrosis</td>
<td>Weiffenbach &amp; McCarthy 1984</td>
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<td>Epilepsy and temporal lobe resection</td>
<td>Martinez et al 1993, West et al 1993</td>
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<tr>
<td>Huntington’s disease</td>
<td>Bylsma et al 1997, Moberg &amp; Doty 1997</td>
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<td>Kallmann’s syndrome</td>
<td>Yousem et al 1993</td>
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<td>Korsakoff’s psychosis</td>
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Several studies suggest that smell loss—particularly in conjunction with other risk factors such as the APOE-ε4 allele—may be a predictor of subsequent development of Alzheimer’s disease, or at least of cognitive dysfunction, in older persons. Furthermore, there is circumstantial evidence that estrogen therapy in later life may protect against or decrease such loss in a manner perhaps analogous to its effects on some measures of cognitive function (Deems et al 1991, Dhong et al 1999, Henderson 1997). In a recent epidemiological study of 1604 nondemented, community-dwelling senior citizens 65 years of age or older, scores on the 12-item Brief-Smell Identification Test™ were a better predictor of cognitive decline over a subsequent 2-year period than scores on a global cognitive test (Graves et al 1999). Persons who were anosmic and possessed at least one APOE-ε4 allele had 4.9 times the risk of having cognitive decline than normosmic persons not possessing this allele (i.e. an odds ratio of 4.9). This is in contrast to the 1.23 times greater risk for cognitive decline in normosmic individuals possessing at least one such APOE allele. When the data were stratified by sex, women who were anosmic and possessed at least one APOE-ε4 allele had an odds ratio of 9.71, compared to an odds ratio of 1.90 for women who were normosmic and possessed at least one allele. The corresponding odds ratios for men were 3.18 and 0.67, respectively. The authors noted, “Therefore, a simple test of olfaction may be more useful in clinical practice to predict cognitive decline than a test of global cognition.”
THE ACCESSORY/VOMERONASAL OLFACTORY SYSTEM

Largely as a result of a series of provocative anatomical and electrophysiological studies (for review, see Monti-Bloch et al. 1998), there has been considerable recent speculation as to whether humans possess a functional accessory olfactory system. Indeed, one study has suggested that human “pheromones” modulate menstrual cycle length via this system (Stern & McClintock 1998). As is discussed below, however, the weight of the evidence is against the notion that humans have a functioning accessory olfactory system, despite the fact that most individuals possess a ventrally-located rudimentary vomeronasal tube near the nasal septum.

General Anatomy

Receptors for the accessory olfactory system are found within the vomeronasal organ (VNO), a tube-like structure surrounded by cartilage at the base of each nasal chamber that is present in most amphibians, reptiles, and mammals (Keverne 1999). It is absent in birds, fishes, and Old World Monkeys. The accessory olfactory system, termed the vomeronasal organ complex by Cooper & Bhatnagar (1976), consists of not only the epithelial tubular VNO, but the vomeronasal duct that opens into the VNO, seromucous glands that secrete into the lumen of the organ, paravomeronasal ganglia lying adjacent to the VNO neuroepithelium, blood vessels adjacent to the epithelium, vomeronasal nerve bundles, the vomeronasal cartilage, the accessory olfactory bulbs, and central connections of the bulbs. The underdevelopment or lack of development of any of these structures results in a nonfunctional VNO (Bhatnagar & Meisami 1998). Based on numerous comparative studies, Bhatnagar & Meisami (1998, p. 467) noted that

No entire class of vertebrates exists in which the VNO is consistently and invariably found in all species within that group in a structurally well-developed and presumably fully functional manner. The mere presence of one or the other vomeronasal structures, almost always the vomeronasal epithelial tubular organ ... does not qualify for a functionally sound sensory organ. In order for the vomeronasal system to be functional, a vomeronasal nerve and accessory olfactory bulb must also be present. It thus appears that variability from complete lack to full development of the vomeronasal organ complex is an inherent evolutionary characteristic of the accessory olfactory system in tetrapods.

In most species that have been examined, the VNO is sexually dimorphic in the adult (larger in males than in females), reflecting the organizational action of sex steroids during the early postnatal period (Segovia & Guillamón 1982). The left and right VNOs are filled with fluid from vomeronasal glands and are separated from one another by the nasal septum. The VNO neuroepithelium, like that of the main olfactory system, is comprised of neural, supporting, microvillar, and
basal cells. As in the case of the main olfactory epithelium, chemicals are sensed by bipolar receptor cells embedded in the epithelium lining the medial concave side of the organ. Unlike the olfactory receptor cells, however, the VNO receptor cells of adult organisms lack cilia, instead containing microvilli upon which seven-transmembrane chemoreceptors are located. The large blood vessels and sinuses along the lateral wall of the VNO, whose engorgement is controlled largely by the autonomic nervous system, can induce a pumplike action for bringing materials into the organ (Meredith et al. 1980). Depending upon the species, entrance of chemicals into the VNO occurs via ducts from the anterior nasal or oral cavities. Stimulus access to the VNO is enhanced in some forms by distinct behaviors, such as the flehmen response—a characteristic lip-curling and snorting behavior in which the external nares are closed. This behavior is frequently seen in cows, horses, deer, and sheep as the male samples the female’s urine stream prior to estrus (Crump et al. 1984).

The axons from the VNO’s sensory neurons project through the vomeronasal nerve, which typically runs along the base of the olfactory bulbs to the accessory olfactory bulb (AOB), the first relay of the system. Recent data suggest that this system, unlike the main olfactory system, may be active only postnatally, at least in mice, because transneuronal tracers do not label mitral cells within the AOB prior to that time (Horowitz et al. 1999). Like the VNO proper, the AOB is sexually dimorphic, being larger in males than in females (Segovia & Guillamón 1993). Dendritic processes of mitral cells within the AOB communicate, via glomeruli, with the axonal terminals of the bipolar receptor cells. Axons of a given class of receptors converge onto numerous glomeruli with the AOB (Rodriguez et al. 1999). The axons of the mitral cells project via a fiber bundle to the “vomeronasal amygdala,” consisting of the medial and posteromedial cortical amygdaloid nuclei and the nucleus of the accessory olfactory tract (Kevetter & Winans 1981). The terminations within the medial nuclei are adjacent, but separate, from those from CN I projections, and this nucleus connects through the stria terminalis to the medial preoptic region of the hypothalamus.

Even though, as mentioned above, nearly all adult humans possess paired VNO-like structures at the base of the septum and paired VNO ducts ~15–20 mm from the posterior aspect of the external nares, the human VNO appears to be a “simple epithelial tube” relative to the well-developed VNO of other species (Smith & Bhatnagar 2000). Recent research indicates that the human VNO appears to develop a pseudo-stratified epithelium and to lose receptor cells and their associated neural elements in the second trimester of pregnancy (Smith & Bhatnagar 2000). The adult human VNO has a comparatively homogeneous epithelium along both its medial and lateral aspects, in contrast to the receptor-rich medial and receptor-free (but vascular-rich) lateral elements of the VNOs of other organisms. Adult human VNOs contain cilia (which are present only in the early embryonic stages of VNO development in most species) and short microvilli, unlike the elongated microvilli typical of other VNOs.
Although the epithelia of human VNOs express immunoreactivity to molecular markers characteristic of neurons [i.e. neuron-specific enolase and protein gene product 9.5], the density of such neurons is comparatively sparse (Takami et al 1993), and antibodies against olfactory marker protein—a marker for functional bipolar receptor cells—have failed to reveal olfactory marker protein–expressing cells in the human VNO. Whereas Takami et al (1993) suggested that the neuron-specific enolase and protein gene product–labeled epithelial cells were vomeronasal receptor neurons, Johnson (1998) has suggested that the immunolabeled cells are likely neuroendocrine cells. The observation that the human VNO is spatially separated from the paraseptal cartilages has led some to question whether it is, in fact, homologous with the VNO of other mammals (Smith & Bhatnagar 2000). Although there is a suggestion of local electrophysiological responsiveness within the human VNO (Monti-Bloch et al 1998), attempts to trace neural connections from this organ to the brain have been uniformly unsuccessful (Bhatnagar et al 1987, Meisami & Bhatnagar 1998). The lack of a VNO nerve and associated accessory olfactory bulb in postnatal humans is in stark contrast to the clearly delineated VNO nerves and accessory olfactory bulbs present in other mammals with functioning VNOs. Because the postnatal human VNO appears to lack basic elements necessary for a functioning VNO (e.g. the elements of the “vomeronasal organ complex” delineated by Cooper & Bhatnagar 1976), it is most likely a nonfunctional entity (Bhatnagar & Meisami 1998).

Transduction Mechanisms

Two large multigene families of G-protein–linked receptors have been identified within the mouse VNO that are only distally related to the multigene family involved in CN I odor receptors (Dulac & Axel 1995, Ryba & Tirindelli 1997), implying that the VNO responds to somewhat different classes of stimuli. The two VNO gene families—V1R and V2R—are also considerably smaller than the gene family involved in CN I odor receptor induction, implying less diversity in the types of stimuli that can be detected. The first of the VNO gene families has G_{iα2} protein–linked receptors located in the apical regions of the VNO, whose cells project to glomeruli within the anterior region of the accessory olfactory bulb (Jia & Halpem 1996). Exposure of male mice to bedding soiled by female mice appears to selectively activate this region of the accessory olfactory bulb (Dudley & Moss 1999). The receptors of the second VNO gene family express G_{oγ} and are located in the basal region of the VNO. The cells containing these receptors project to glomeruli in the posterior accessory olfactory bulb. Like olfactory receptor neurons, each bipolar receptor cell appears to express only one type of receptor (Dulac & Axel 1995). Recent data suggest that the two classes of receptors may differentially respond to volatile and non-volatile agents (Krieger et al 1999). Thus, upon stimulation with lipophilic volatile agents from mouse urine, only G_{i} proteins were activated. Upon stimulation
with a major urinary protein of the lipocalin superfamily, only $G_{o}$ proteins were activated.

Electrophysiologically, the cells within the VNO tend to fire in a sustained manner, in contrast to the cells within the main olfactory epithelium, which fire in single pulses or bursts (Døving & Trotier 1998). The sustained firing may maximize the summed neural activity induced on central structures from even brief exposures to biologically active chemicals, allowing for the induction of endocrine effects (Keverne 1999).

**Vomeronasal Organ Cell Regeneration**

Considerably less is known about the regenerative properties of the VNO than those of the primary olfactory mucosa. After unilateral transection of the vomeronasal nerves in the adult hamster, the receptor cells degenerate, reaching 16% of the original number 6 days after the transection. Although cell numbers return to normal after 40 to 60 days, thickness of the epithelium never recovers beyond 70% of the control thickness (Ichikawa et al 1998). From 12 to 32 weeks after transection, less than a third of projection fibers appear to make synaptic contacts within the anterior olfactory nucleus, implying that full recovery from total transection does not occur (Ichikawa 1999).

**Recent Studies of Vomeronasal Organ Function**

It has been known for some time that the VNO plays a role, either exclusively or in combination with CN I, in a number of reproduction-related phenomena. Data, primarily from rodents, suggests VNO participation in a variety of endocrine responses and social related behaviors, including (a) estrous synchrony or regulation (Johns et al 1978), (b) blockage of ova implantation following exposure to “strange” (i.e. nonstud) male odor (Lloyd-Thomas & Keverne 1982), (c) activation of reproduction and male-induced sexual receptivity (Wysocki et al 1991, Rajendren et al 1990), (d) acceleration of puberty (Lomas & Keverne 1982), (e) male copulatory behavior (Wekesa & Lepri 1994, Winans & Powers 1974), (f) nursing behavior (Saito et al 1990), (g) attraction to odors of the opposite sex (Romero et al 1990), and (h) various forms of male agonistic behavior (Wekesa & Lepri 1994).

Knowledge of VNO activity across a wide range of species is still limited. Recent data suggest that the VNO does not mediate a widely touted “pheromonal” effect in pigs and that, even within the same genus of vole, the VNO may have opposite effects on reproductive behaviors. Thus, Dorries et al (1997) have demonstrated that inactivating the VNO has no influence on either the female pig’s attraction to androstenone, one of the few mammalian secretions that has been widely described as a pheromone, or the facilitative effects of this steroid on receptive standing behavior (lordosis). If one accepts the notion that, in fact, mammalian pheromones exist (which is debatable), and that androstenone is a pheromone, then this observation would throw into question the concept that the VNO can
be considered, in a general sense, as “the” pheromone detector in mammals (Belluscio et al 1999). Although the VNO appears to mediate the induction of behavioral estrus in prairie voles (Microtus ochrogaster) by male odors (Wysocki et al 1991), this is not the case in meadow voles (M. pennsylvanicus), a species believed to be a spontaneous ovulator. Meek et al (1994) removed the VNO from nulliparous female meadow voles maintained under long photoperiods simulating summer (14 h light: 10 h dark) and short photoperiods simulating winter (10 h light: 14 h dark). Under the winter lighting condition, the VNO removal had no influence on either the percentage of animals mating or the latency to copulation. Under the summer lighting condition, removal of the organ actually increased the percentage of the females mating and decreased the latency to mating after pairing.

Re-establishment of mating behavior in the male hamster whose VNO has been removed occurs following injection of gonadotropin-releasing hormone (GnRH), implying that stimulation of the VNO is needed to produce GnRH at levels high enough to allow for the activation of sexual behavior (Meredith & Howard 1992). GnRH’s influences may be mediated independently of the pituitary, however, since the GnRH analog, AcLHRH5-10, which does not induce luteinizing hormone release, facilitates mating behavior in hamsters whose VNOs have been removed (Femandez-Fewell & Meredith 1995). Bilateral lesions within the corticomedial nucleus of the amygdala (a major projection center of the VNO) eliminates or greatly attenuates male mating behavior, and mitigates investigatory sniffing and licking behavior directed toward the female hamster’s anogenital region (Lehman et al 1980). This result is not secondary to decreases in testosterone, as testosterone injections do not restore normal mating behavior (Lehman et al 1980). Whether GnRH restores mating behavior in rats with such lesions is apparently not known but would seem probable.

CONCLUSIONS

Remarkable progress has been made in the past decade in understanding the function of both the main and accessory olfactory systems. The development of proliferation of practical and reliable olfactory tests has spurned an awakening on the part of the medical community as to the important role of olfaction in a wide range of clinical disorders, and has led to the realization that olfactory loss is likely the first clinical sign of some neurodegenerative diseases. The application of new technologies, including those of molecular biology and functional imaging, are beginning to unravel the mysteries of both peripheral and central coding, and should lead, within the next decade, to a rather complete understanding of olfactory system function. Studies of vomeronasal function are continuing in a wide range of species, and the complexity of behaviors influenced by the accessory olfactory system is now beginning to be realized.
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GLOSSARY OF BASIC ANATOMICAL TERMS

**Accessory olfactory system:** The chemosensory system that includes the paired vomeronasal organs located on each side of the ventral nasal septum, the vomeronasal nerve, the accessory olfactory bulb, and central connections. In mammals, this system has been implicated in numerous reproduction-related processes. Although humans exhibit a rudimentary set of vomeronasal organs, they lack the other neural components of the system.

**Basal cells:** Cells located at the base of the olfactory and vomeronasal organ epithelia from which the other cell types of the epithelia arise. In the olfactory epithelium, such cells are divided into globose (light) and horizontal (dark) basal cells, the former of which appear to give rise to both neural and nonneural elements of the epithelium.

**Bowman's glands:** Secretory glands within the olfactory epithelium that produce most of the mucus of this region. These glands contain xenobiotic metabolizing enzymes that protect the region from toxic and other insults and may aid in deactivating odorants.

**Cribriform plate:** A thin section of the ethmoid bone that separates the upper nasal cavity from the brain cavity. The olfactory nerve fibers project through this bone from the nasal cavity to the brain.

**Main olfactory system:** The chemosensory system that is most commonly associated, in vertebrates, with the sense of smell. This system is comprised of the olfactory receptor cells, the paired olfactory bulbs and tracts at the base of the brain, and central processing structures, including regions of the piriform, entorhinal, and orbitofrontal cortices.

**Microvillar cells:** Bell-shaped cells located at the surface of the olfactory epithelium that project microvilliæ into the mucus. Although these cells appear to possess axons that extend through the cribriform plate into the olfactory bulb, it is not known whether they are chemoreceptive.

**Nasal turbinates:** The projections of thin bone from the lateral wall of the nasal cavity that are covered by highly vascularized mucous membrane and, in the human, are designated as superior, middle, or inferior. Also termed nasal conchæ. The engorgement of these structures, which aid in the cleansing, warming, and humidification of the nasal airstream, is altered by environmental
(e.g. air temperature) and organismal (e.g. hormones) factors. In humans, much of the olfactory epithelium is located on the superior and middle nasal turbinates.

**Nervus terminalis**: A plexus of nerves and ganglia that ramify throughout the nasal epithelium before crossing the olfactory mucosa and coursing through the cribriform plate medial to the olfactory and vomeronasal nerves. Also known as the terminal nerve or cranial nerve 0. Noted for its high content of GnRH (a hormone that has major influences on the reproductive organs), the nervus terminalis plays a significant role in reproduction in some species.

**Olfactory bulbs**: Paired oval structures at the base of the brain from which the olfactory tracts arise and that serve as the first relay station of the olfactory system. These structures, which have distinct layers of neurons and related cells, are involved in the initial processing of olfactory information.

**Olfactory cortex**: Regions of the cerebral cortex that interpret and transmit information coming in from lower centers. The olfactory cortex is divided into the primary olfactory cortex (i.e. brain regions receiving information from the olfactory bulb, such as the entorhinal, piriform, and periamygdala cortices) and secondary olfactory cortex, most notably the orbitofrontal cortex.

**Olfactory epithelium**: The sensory neuroepithelium that contains the olfactory receptor cells and that lines the upper recesses of the nasal cavity, including, in humans, sectors of the superior and middle turbinates.

**Olfactory receptor cells**: Ciliated bipolar neurons within the olfactory neuroepithelium that possess the olfactory receptors where initial odor reception takes place. These cells are both the receptor cell and the first-order neuron of the olfactory system, and project their axons from the nasal cavity into the brain. Humans have ~six million olfactory receptor cells that, in aggregate, comprise cranial nerve I.

**Septal organ**: A small region of neuroepithelial tissue found on the anterior ventral nasal septum in some species, also known as the organ of Masera. This structure, whose epithelium is similar to that of the main olfactory system, sends axons to a small sector of the olfactory bulb and is believed by some to be the first chemosensory structure to be activated by incoming molecules.

**Trigeminal chemosensory system**: Those branches of cranial nerve V whose free nerve endings, largely located in mucosal tissue within the nose and sinuses, oral cavity, eyelids, and cornea, can be activated by chemicals. Somatosensory sensations, such as burning, stinging, sharpness, and coolness, are produced by chemical activation of fibers within this system.

**Vomeronasal Organ**: A tubelike structure located adjacent to the anterior ventral nasal septum of most vertebrates (also termed Jacobson’s organ). This organ contains the receptors that activate the other components of the accessory olfactory system. Depending upon the species, the vomeronasal organ typically has openings into either the nasal cavity or the oral cavity, and is responsive to both liquid-borne and airborne chemical stimuli.
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