

## Anatomy and physiology

The sense of smell, viewed as the sentinel of the brain by Macdonald Critchley (Critchley, 1986), largely determines the flavor of foods and beverages, and provides an early warning system for the detection of such hazards as fire, leaking natural gas, and spoiled food. Aside from playing a critical role in safety, nutrition, and quality of life, this important sense provides an index of the health of sectors of the brain not discernible by other means. Thus, decreased smell function can signify the early development of neuropathology within limbic structures associated with Alzheimer's disease and idiopathic Parkinson's disease – neuropathology that can occur several years before the onset of other clinical signs (see Chapter 4). Before undergoing the ravages of old age and associated neural dysfunction, humans are exquisitely sensitive to odors, detecting some substances, such as mercaptans added to odorize natural gas, in the parts-per-billion range.

Despite such importance, olfaction has been neglected by most neurologists, with the majority failing even to test its function. Fortunately this has been changing in recent years, in part because of (1) the development and proliferation of practical quantitative smell tests, (2) a better understanding of its association with neurodegenerative diseases, (3) the elucidation of its transduction mechanisms, and (4) a broader appreciation of its general importance to human health and well-being.

In this chapter we describe the anatomy and physiology of the olfactory system, as well as a number of factors which influence its normal function. Emphasis is placed on the system's complex and dynamic nature, including its unique regenerative properties and critical associations with brain structures related to emotion and memory. The influences of diseases on olfactory function are discussed in Chapters 3 and 4.

### The nasal cavity

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For odorant molecules to reach the olfactory receptors, they must first pass through the upper recesses of the nasal cavity, the first part of the respiratory

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passages. This highly vascularized cavity is separated into two chambers by a partition, the nasal septum. Three or, more rarely, four structures, termed nasal turbinates, project from the lateral wall of each side of the nose into the cavity. These structures receive their blood supply from branches of the sphenopalatine artery, the end artery of the internal maxillary branch of the external carotid artery (Lee *et al.*, 2002). The lymphatic system of the nasal mucosa drains into the superficial cervical lymph nodes, which drain into the posterior cervical lymph nodes. Medial to each turbinate is a cleft or meatus. It is the most superior of these clefts, the olfactory cleft, through which air passes to reach the olfactory receptor region. These features and parts of the olfactory forebrain are displayed in Figure 1.1.

The nasal turbinates, particularly the inferior and middle, are richly endowed with a network of tortuous veins that can rapidly swell with blood. Such engorgement dramatically alters nasal passage volume, influencing the amount of air that reaches the olfactory cleft and respiratory processes in general. When the turbinates are moderately distended, more air is delivered to the olfactory cleft than when they are markedly engorged or disengorged (Schneider & Wolf, 1960). In the human, 5–15 percent of the inhaled air-stream is diverted to the receptor region, depending upon such engorgement, the strength of sniffing, idiosyncratic aspects of nasal cavity anatomy, the thickness of the mucus, and the size and shape of the nasal valve (Keyhani *et al.*, 1995). Exercise, hypercapnia, and increased sympathetic tone are among the factors that constrict turbinate engorgement, whereas cold air, irritants, hypocapnia, and increased parasympathetic tone are among those that increase such engorgement (Jones, 2001). Short repetitive sniffs appear to be less efficient than long sustained sniffs in optimizing olfactory sensitivity and the delivery of odorants into the human olfactory cleft (Laing, 1983; Mainland & Sobel, 2006; Zhao *et al.*, 2004, 2006). High flow rates favor absorption of hydrophilic compounds, whereas low flow rates favor absorption of hydrophobic substances (Mozell *et al.*, 1991).

It is now known that most people experience changes in the relative engorgement of each side of the nose over time (Haight & Cole, 1984). In some individuals, such changes are coordinated, resulting in periodic shifts of relative left–right airflow. These side-to-side fluctuations have been reported to have period lengths ranging from one to five hours in adults and to be absent in children. Although this “nasal cycle” has been said to be present in up to 80 percent of adults, recent studies suggest that this may be an overestimate (Flanagan & Eccles, 1997). Thus, if one accepts the commonly held definition of cycle (regular periodicity) and assumes that 180° phase differences are required for the left–right engorgement periods, very few humans have a true nasal cycle. In one study using autocorrelation analysis, for example, only 9 (15 percent) of 60 subjects exhibited the classical nasal cycle, 28.3 percent exhibited parallel cycles (i.e., left–right engorgement changes

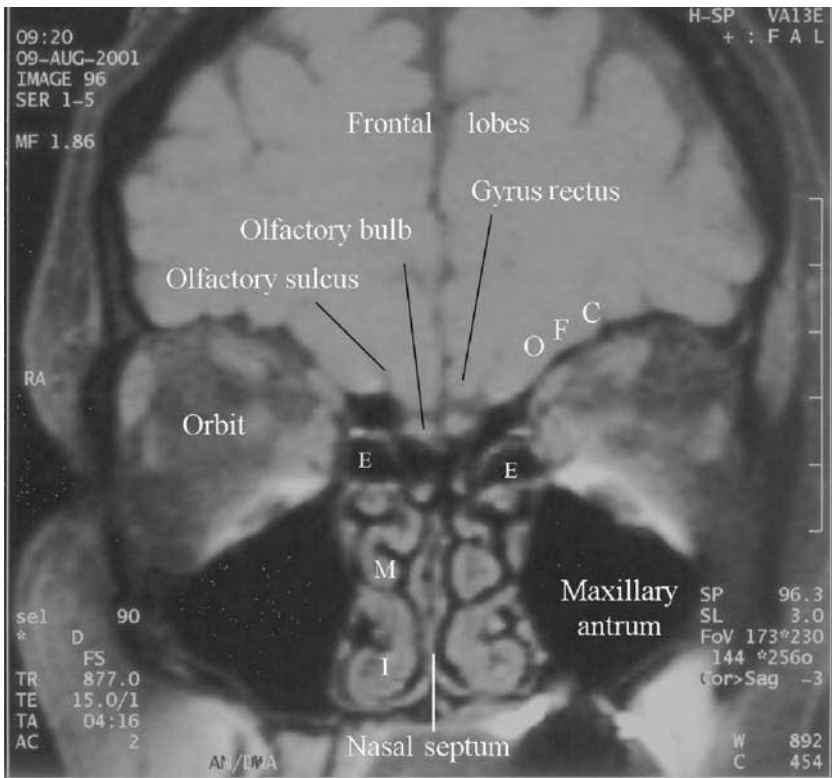


Figure 1.1 MRI scan (coronal, T1 weighted) in healthy 45-year-old lady showing frontal lobes; orbits; olfactory bulbs, olfactory sulcus and gyrus rectus. OFC is the orbitofrontal cortex. Letter “E” indicates part of the ethmoid sinuses, which are frequently honeycomb structures. Letter “I” is the right inferior turbinate; “M” is the right middle turbinate. The superior turbinate and infundibulum are not clearly shown due to the posterior coronal section. (Reproduced with permission from Hawkes, 2002. Copyright © 2002, Elsevier.)

that are in phase), 23.3 percent exhibited hemicycles (i.e., only one side showing engorgement fluctuations over time), and 33.3 percent were acyclic (Mirza *et al.*, 1997). Another study, also based upon statistical criteria, found a classic nasal cycle in only 2 of 16 (13 percent) adults evaluated. Hemicycles were observed in seven (44 percent) (Gilbert & Rosenwasser, 1987).

Regardless of its periodicity, left–right fluctuations in nasal engorgement are claimed to be an overall index of autonomic tone (Werntz *et al.*, 1983). When the left nasal chamber is more congested than the right, general sympathetic activity predominates over parasympathetic activity. When the

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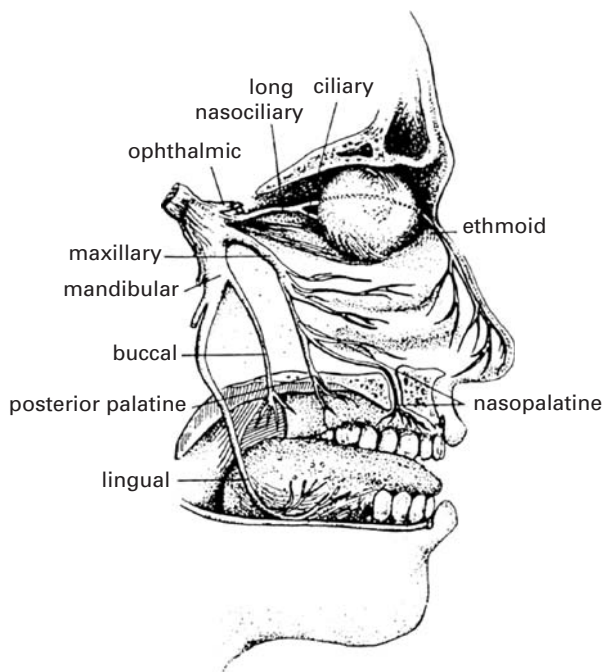


Figure 1.2 Schematic diagram of the branches of the trigeminal nerve that innervate the nasal, oral, and ocular epithelia. (From Bryant and Silver, 2000. Copyright © 2000, Wiley-Liss. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

right nasal chamber is more engorged than the left, the opposite is the case. Importantly, the relative degree of left–right engorgement correlates with such measures as: (1) the relative electroencephalographic (EEG) activity of the two cerebral hemispheres (Werntz *et al.*, 1983); (2) rapid eye movement (REM) and non-REM sleep activity patterns (Goldstein *et al.*, 1972); (3) verbal and spatial cognitive processing (Klein *et al.*, 1986); and (4) asymmetrical activity in paired body organs, including the release of hormones from paired glands such as the adrenal glands (Shannahoff-Khalsa *et al.*, 1996). Olfactory thresholds tend to be lower on both sides of the nose during the heightened sympathetic component of engorgement, that is, when the left nasal chamber is more occluded (Frye & Doty, 1992). Interestingly, when subjects sniff a two-odor mixture composed of a hydrophobic and a hydrophilic odor, the hydrophobic element of the mixture is better perceived through the low-flow nostril and the hydrophilic element through the high-flow nostril (Sobel *et al.*, 1999a).

The general somatic nerve supply to the nose derives from branches of the trigeminal nerve (Doty & Cometto-Muniz, 2003), whereas the autonomic

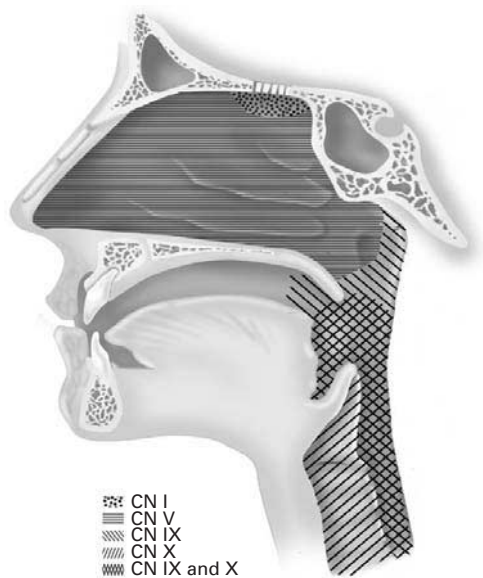


Figure 1.3 A schematic of the regions within the nasal and oral cavities innervated by several cranial nerves that can be stimulated by some odorants and irritants. CN I, olfactory nerve; CN V, trigeminal nerve; CN IX, glossopharyngeal nerve; CN X, vagus; CN VII innervates the taste buds in the anterior tongue and is not shown in this diagram. The cross-hatched regions represent areas of overlap between CN IX and CN X. CN V also innervates the region innervated by CN I. CN I may extend farther down onto the middle turbinate than depicted here. (Copyright © 2002, Richard L. Doty.)

supply to the nose comes from the sphenopalatine ganglion. The anterior and posterior ethmoid nerves, which are branches of the nasociliary nerve (ophthalmic division of V), supply the upper part of the nasal cavity (Figure 1.2). The posterior part of the nasal cavity is fed by the nasopalatine nerve, a branch of the maxillary nerve. The autonomic supply to the nose comes from the sphenopalatine ganglion.

Some airborne odorants and other chemicals are capable of stimulating trigeminal free nerve endings distributed throughout the nasal mucosa, as well as trigeminal and other sensory nerve endings dispersed in other regions of the throat and mouth (Figure 1.3). Examples of sensations resulting from such stimulation are warmth, coolness, and sharpness (Doty *et al.*, 1978). These somatosensory sensations should not be confused with odors, although they can contribute to the overall appreciation of an odor.

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Figure 1.4 Scanning electron micrograph of surface of human olfactory epithelium showing where thin parts of olfactory cilia form a blanket covering the epithelial surface. Asterisk indicates opening into duct of a Bowman's gland. Bar, 10  $\mu\text{m}$ . (From Menco and Morrison, 2003. With permission.)

### The olfactory epithelium

In the human nose, there are an estimated six million specialized olfactory receptor cells per nostril (Moran *et al.*, 1982). The receptor cells are embedded in a matrix of supporting cells within a pseudostratified columnar epithelium located high in the nasal chamber (Figure 1.4, Figure 1.5, Figure 1.6). This neuroepithelium covers the cribriform plate and lines sectors of the superior septum, superior turbinate, and, to a lesser extent, the anterior portion of the middle turbinate. The existence of some olfactory receptor cells (ORC) on the middle turbinate (Leopold *et al.*, 2000) is a useful aspect of applied anatomy for those wishing to biopsy ORC for culture, histology, or patch clamp studies, as it is more accessible and less risky to

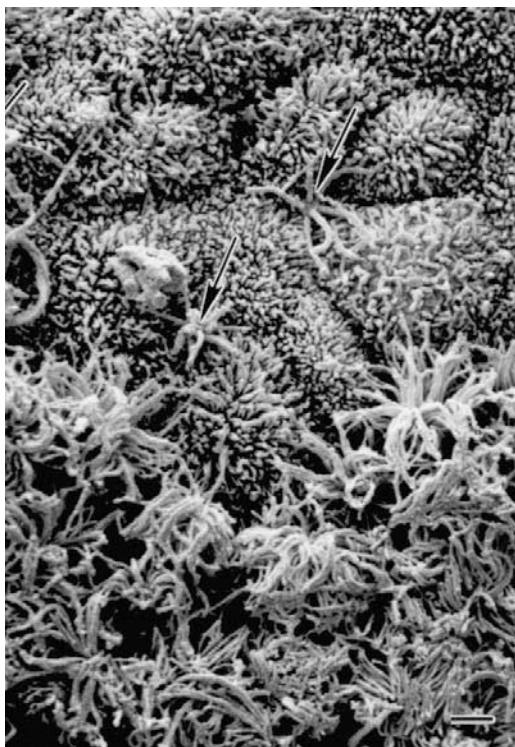
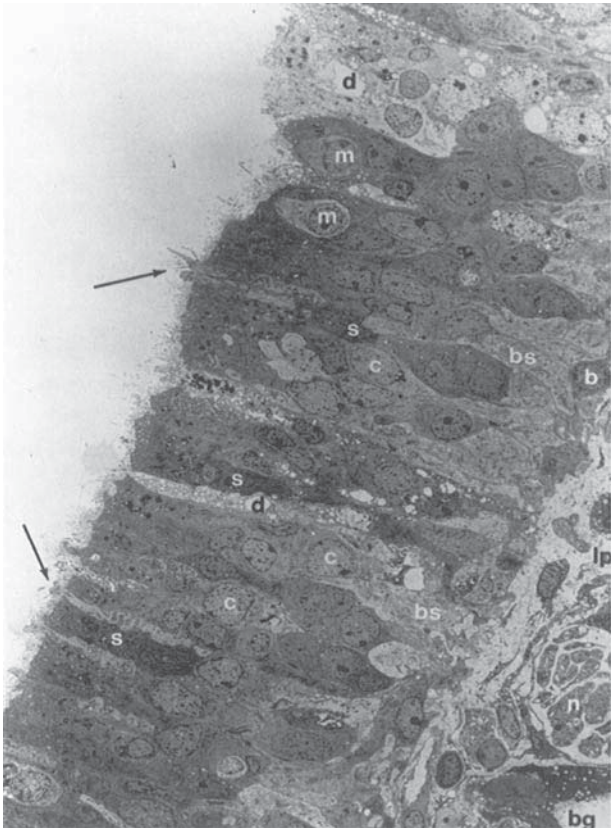


Figure 1.5 A transition region between the human olfactory (bottom half) and respiratory (top half) epithelia. Arrows signify two examples of olfactory receptor cell dendritic endings with cilia. (From Menco and Morrison, 2003. With permission.)

sample than the main olfactory area. Whilst most of the bony and cartilaginous structures within the nasal cavity, including the turbinates, are covered with a mucus-secreting respiratory epithelium, the olfactory region is covered with a distinctly different epithelium whose mucus is mainly derived from specialized glands, termed “Bowman’s glands” (for review, see Menco & Morrison, 2003).

The bipolar olfactory receptor cells serve as the first-order neurons of the system, and their central limbs project directly from the nasal cavity to the olfactory bulb without synapse, making them a major conduit for central nervous system (CNS) viral and xenobiotic invasion, as described in Chapter 4. These receptor cells form tight junctions with adjacent non-neural cells. The apical end of each cell has a knob-like protrusion from which receptor-containing cilia project into the mucus (Figure 1.7). Embryologically, these cells are derived from the olfactory placode and are thus of CNS origin (Chuah *et al.*, 2003). Their somata are found at all levels within the

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**Figure 1.6** Low-power electron photomicrograph of cross-section of the human olfactory neuroepithelium depicting the four major types of cells: bipolar receptor cells (arrows point to cilia at dendritic knob; c, cell body), microvillar cells (m), sustentacular cells (s), and basal cells (b); bg, Bowman's gland; lp, lamina propria; n, collection of axons within an ensheathing cell; d, degenerating cells; bs, basal cell undergoing mitosis. (Photo courtesy of Dr. David Moran, Longmont, Colorado.)

epithelium, with the somata of the older cells being closer to the mucosal surface than those of more recently differentiated cells. The axons of the bipolar olfactory cells are extremely small ( $\sim 0.2 \mu\text{m}$  in diameter), making them among the thinnest and slowest conducting ( $\sim 1 \text{ m/s}$ ) axons in the nervous system. In humans, the cilia number, on average,  $\sim 25$  per cell, whereas in other species, such as the dog, this can number in the hundreds. Although the olfactory cilia contain the familiar  $9+2$  arrangement of microtubules, i.e., two central microtubules surrounded by nine outer doublet microtubules, they lack the muscle-like dynein arms required for

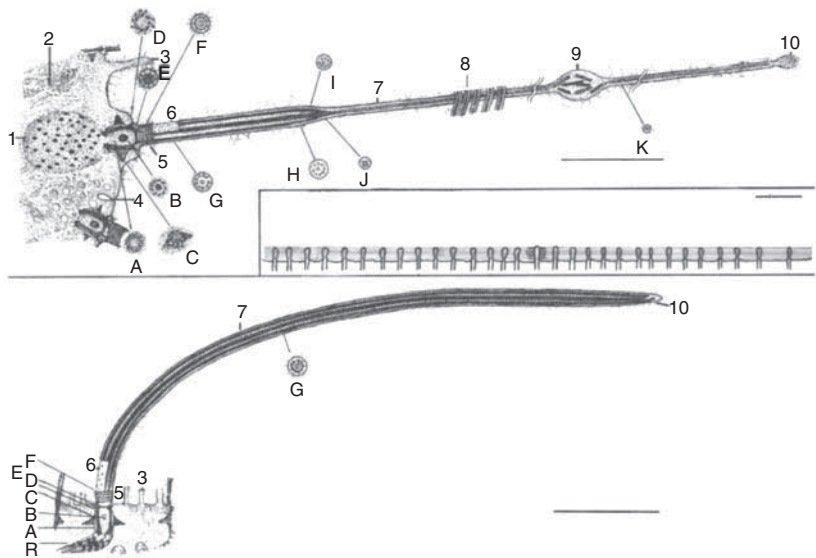


Figure 1.7 Diagram of mammalian olfactory (top) and respiratory (bottom) cilia. Features of the two diagrams have been drawn to scale. The olfactory cilium is interrupted at two places, indicating that the cilia are actually much longer. A–E, basal body cross-sections; F–H, cross-sections through proximal regions of olfactory cilia (top) and homologous regions of respiratory cilia (bottom); I–K, cross-sections through distal parts of olfactory cilium; R, striated rootlet of respiratory cilium; 1, fibrogranular microtubule pool (cilium precursor pool); 2, microtubules inside dendritic endings; 3, microvilli of dendritic endings (sparse) and of ciliated respiratory cells; 4, coated vesicles; 5, ciliary necklaces (seven strands for olfactory cilia, five strands for respiratory cilia); 6, ciliary membranes studded with membrane particles reflecting proteins which are more numerous in olfactory than respiratory cilia; 7, nearby glycocalyx; 8, bundle of tapers of other, nearby, cilia; 9, vesiculated expansion along distal part of cilium; 10, ciliary tips which in the case of olfactory cilia terminate in a small vesicle. The inset demonstrates that the cilia of one receptor cell dendrite can extend over about 15 other endings. Top and bottom bars = 1  $\mu\text{m}$ ; center bar = 10  $\mu\text{m}$ . (From Menco and Morrison, 2003. With permission.)

motility (Figure 1.7; Menco & Morrison, 2003). Hence, they do not beat synchronously, unlike the cilia of the respiratory epithelium, and simply waft in the mucus.

The supporting cells, also termed “sustentacular cells,” are predominant within the olfactory epithelium. These relatively large cells insulate the receptor cells from one another, regulate mucus microcomposition, deactivate odorants, and protect the epithelium from foreign agents. Although these cells lack cilia, they project many microvillae into the mucus.

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In addition to the olfactory receptor and supporting cells, the olfactory epithelium harbors cells which line the glands and ducts of the Bowman's glands, microvillar cells, and two types of basal cells (namely, horizontal and globose basal cells), as well as other cellular elements (Figure 1.6). The microvillar cells, whose function remains poorly understood, resemble so-called brush cells of the upper and lower airways of many species. They are located at the epithelial surface and, like the supporting cells, extend microvillae from their apical surfaces into the olfactory mucus (Moran *et al.*, 1982). In the human, they occur in about a 1:10 ratio with the bipolar receptor cells, numbering around 600 000 in an intact epithelium. The horizontal (dark) and globose (light) basal cells are located near the basement membrane and are stem cells from which other classes of cells arise (Figure 1.6).

In addition to odorants, numerous volatile compounds, as well as nonvolatile ones that adsorb from small particles in the air, are readily taken up by the nasal mucosa (Schlesinger, 1985; Stott *et al.*, 1986). For example, herbicides such as dioxins (Gillner *et al.*, 1987) and chlorthiamid (Brittebo *et al.*, 1991) are selectively absorbed by the olfactory epithelium, causing damage to the cells. Compounds absorbed by the nasal mucosa are actively metabolized in situ. In some cases they are detoxified, but in other cases they are transformed into metabolites of greater toxicity or carcinogenicity (Bond, 1986; Dahl, 1986). Whilst the high concentration of P450 in hepatic microsomes is well known, microsomes in the olfactory epithelium also have high levels of P450 mono-oxygenases, as shown, for example, in the rat (Hext & Lock, 1992) and rabbit (Ding & Coon, 1990). Supporting cells, as well as the acinar and duct cells of Bowman's glands, are particularly endowed with such xenobiotic metabolizing enzymes (Ding & Dahl, 2003), serving to metabolize agents that become absorbed in the olfactory mucus. More than 10 different P450s have been identified in mammalian olfactory mucosa, including members of the CYP1A, 2A, 2B, 2C, 2E, 2G, 2J, 3A, and 4B subfamilies (Ding & Dahl, 2003). Several P450s are preferentially expressed in this mucosa, including CYP2G1. The P450 levels are sometimes in excess of those in the liver, depending on the particular subtype. Compounds that have been shown to be metabolized in vitro by the nasal P450 dependent mono-oxygenase system include nasal decongestants, essences, anesthetics, alcohols, nicotine, cocaine, and many nasal carcinogens (Dahl, 1988).

When the olfactory epithelium is damaged, the same type of basal cell, most likely a globose cell, gives rise to both neural and non-neural cells, allowing for the replacement of damaged receptors (Huard *et al.*, 1998). Although at one time it was believed that the sensory neurons of the olfactory epithelium are automatically and continuously replaced by the differentiating basal cells over the course of a month or so, we now know this is not true. Thus, long-lived receptor cells have been observed in rats (Hinds *et al.*, 1984), and regulatory mechanisms have been identified that alter the timing and