

# OLFACTORY SENSE

Part of "Chapter 12 - DISORDERS OF SMELL AND TASTE"

## **Anatomic and Physiologic Considerations**

Nerve fibers subserving the sense of smell have their cells of origin in the mucous membrane of the upper and posterior parts of the nasal cavity (superior turbinates and nasal septum). The entire olfactory mucosa covers an area of about 2.5 cm<sup>2</sup> and contains three cell types—the olfactory or receptor cells (which number between 6 and 10 million in each nasal cavity); sustentacular or supporting cells; which maintain the electrolyte (particularly K) levels in the extracellular milieu; and basal cells, which are stem cells and the source of both the olfactory and sustentacular cells during regeneration. The olfactory cells are actually bipolar neurons. Each of these cells has a peripheral process (the olfactory rod), from which project 10 to 30 fine hairs, or cilia. These hair-like processes, which lack motility, are the sites of olfactory receptors. The central processes of these cells, or *olfactory fila*, are very fine (0.2 mm in diameter), unmyelinated fibers that converge to form small fascicles enwrapped by Schwann cells that pass through openings in the cribriform plate of the ethmoid bone into the olfactory bulb (Fig. 12-1). Collectively, the central processes of the olfactory receptor cells constitute the *first cranial, or olfactory, nerve*. Notably, this is the only site in the organism where neurons are in direct contact with the external environment. The epithelial surface is covered by a layer of mucus, which is secreted by tubuloalveolar cells (Bowman's glands) and within which there are immunoglobulins A and M, lactoferrin, and lysoenzyme as well as odorant-binding proteins. These molecules are

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thought to prevent the intracranial entry of pathogens via the olfactory pathway (Kimmelman).

**Figure 12-1** *Diagram illustrating the relationships between the olfactory receptors in the nasal mucosa and neurons in the olfactory bulb and tract. Cells of the anterior olfactory nucleus are found in scattered groups caudal to the olfactory bulb. Cells of the anterior olfactory nucleus make immediate connections with the olfactory tract. They project centrally via the medial olfactory stria and to contralateral olfactory structures via the anterior commissure. Inset: diagram of the olfactory structures on the inferior surface of the brain (see text for details).*

In the olfactory bulb, the receptor-cell axons synapse with granule cells and mitral cells (triangular, like a bishop's miter), the dendrites of which form brush-like terminals or olfactory glomeruli (Fig. 12-1). Smaller, so-called tufted cells in the olfactory bulb also contribute dendrites to the glomerulus. Approximately fifteen thousand olfactory-cell axons converge on a single glomerulus. This high degree of convergence is thought to account for an integration of afferent information. The mitral and tufted cells are excitatory; the granule cells—along with centrifugal fibers from the olfactory nuclei, locus ceruleus, and piriform cortex—inhibit mitral cell activity. Presumably, interaction between these excitatory and

inhibitory neurons provides the basis for the special physiologic aspects of olfaction.

The axons of the mitral and tufted cells form the olfactory tract, which courses along the olfactory groove of the cribriform plate to the cerebrum. Lying caudal to the olfactory bulbs are groups of cells that constitute the anterior olfactory nucleus (Fig. 12-1). Dendrites of these cells synapse with fibers of the olfactory tract, while their axons project to the olfactory nucleus and bulb of the opposite side; these neurons are thought to function as a reinforcing mechanism for olfactory impulses.

Posteriorly, the olfactory tract divides into medial and lateral olfactory striae. The medial stria contains fibers from the anterior olfactory nucleus, which pass to the opposite side via the anterior commissure. Fibers in

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the lateral stria originate in the olfactory bulb, give off collaterals to the anterior perforated substance, and terminate in the medial and cortical nuclei of the amygdaloid complex and the prepiriform area (also referred to as the lateral olfactory gyrus). The latter represents the *primary olfactory cortex*, which in humans occupies a restricted area on the anterior end of the parahippocampal gyrus and uncus (area 34 of Brodmann; see Fig. 22-1 and Fig. 22-2). Thus olfactory impulses reach the cerebral cortex without relay through the thalamus; in this respect also, olfaction is unique among sensory systems. From the prepiriform cortex, fibers project to the neighboring entorhinal cortex (area 28 of Brodmann) and the medial dorsal nucleus of the thalamus; the amygdaloid nuclei connect with the hypothalamus and septal nuclei. The role of these latter structures in olfaction is not well understood, but presumably they subserve reflexes related to eating and sexual function. As with all sensory systems, feedback regulation occurs at every point in the afferent olfactory pathway.

In quiet breathing, little of the air entering the nostril reaches the olfactory mucosa; sniffing carries the air into the olfactory crypt. To be perceived as an odor, an inhaled substance must be volatile—i.e., spread in the air as very small particles—and soluble in water. Molecules provoking the same odor seem to be related more by their shape than by their chemical quality. When a jet of scented vapor is directed to the sensory epithelium, as by sniffing, a slow negative potential shift called the *electro-olfactogram* (EOG) can be recorded from an electrode placed on the mucosa. The conductance changes that underlie the receptor potential are induced by molecules of odorous material dissolved in the mucus overlying the receptor. The transduction of odorant stimuli to electrical signals appears to be mediated in part by a GTP-dependent adenylyl cyclase (“G protein”); like other cyclic AMP pathways, it utilizes an intracellular second messenger, but in the case of olfaction, the responsible molecule has not been definitely identified. There follow conformational changes in transmembrane receptor proteins and a series of intracellular biochemical events that generate axon potentials. Intensity of olfactory sensation is determined by the frequency of firing of afferent neurons. The quality of the odor is thought to be provided by “cross-fiber” activation, since the individual receptor cells are responsive to a wide variety of odorants and exhibit different types of responses to stimulants—excitatory, inhibitory, and on-off responses have been obtained. The olfactory potential can be eliminated by destroying the olfactory receptor surface or the olfactory filaments. The loss of EOG occurs 8 to 16 days after severance of the nerve; the receptor cells disappear, but the

sustentacular cells are not altered. Most significant is the fact that, as a result of division of the basal cells of the olfactory epithelium, the olfactory receptor cells are constantly dying and being replaced by new ones. In this respect the chemoreceptors, both for smell and for taste, are unique, constituting the only examples of neuronal regeneration in humans.

The trigeminal system also participates in chemesthesia through undifferentiated receptors in the nasal mucosa. These receptors have little discriminatory ability but a great sensitivity to all irritant stimuli. The trigeminal afferents also release neuropeptides that result in hypersecretion of mucus, local edema, and sneezing. Finally, it should be noted that stimulation of the olfactory pathway at sites other than the receptor cells may also induce olfactory experiences.

The olfactory system adapts quickly to the sensory stimulus, and for sensation to be sustained, there must be repeated stimulation. The olfactory sense differs from other senses in yet another way. It is common experience that an aroma can restore long-forgotten memories of complex experiences. That olfactory and emotional stimuli are strongly linked is not surprising in view of their common roots in the limbic system. Yet the ability to recall an odor is negligible in comparison with the ability to recall sounds and sights. As Vladimir Nabokov has remarked: "Memory can restore to life everything except smells."

### ***Clinical Manifestations***

Disturbances of olfaction may be subdivided into four groups, as follows:

1. Quantitative abnormalities: loss or reduction of the sense of smell (anosmia, hyposmia) or, rarely, increased olfactory acuity (hyperosmia)
2. Qualitative abnormalities: distortions or illusions of smell (dysosmia or parosmia)
3. Olfactory hallucinations and delusions caused by temporal lobe disorders or psychiatric disease
4. Higher-order loss of olfactory discrimination (olfactory agnosia)

### **Anosmia (Loss of Sense of Smell)**

This is the most frequent clinical abnormality, and, if unilateral, will usually not be recognized by the patient. Unilateral anosmia can sometimes be demonstrated in the hysterical patient on the side of anesthesia, blindness, or deafness. Bilateral

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anosmia, on the other hand, is a not uncommon complaint, and the patient is usually convinced that the sense of taste has been lost as well (*ageusia*). This calls attention to the fact that taste depends largely on the volatile particles in foods and beverages, which reach the olfactory receptors through the nasopharynx, and that the perception of flavor is a combination of smell, taste, and tactile sensation. This can be proved by demonstrating that such patients are able to distinguish the elementary taste sensations (sweet, sour,

bitter, and salty). The olfactory defect can be verified readily enough by presenting a series of nonirritating olfactory stimuli (vanilla, peanut butter, coffee, tobacco, etc.), first in one nostril, then in the other, and asking the patient to sniff and identify them. If the odors can be detected and described, even if they cannot be named, it may be assumed that the olfactory nerves are relatively intact (humans can distinguish many more odors than they can identify by name). Ammonia and similar pungent substances are unsuitable stimuli because they do not test the sense of smell but have a primary irritating effect upon the free nerve endings of the trigeminal nerves.

A more elaborate scratch and sniff test has been developed and standardized by Doty and colleagues (University of Pennsylvania Smell Identification Test). In this test the patient attempts to identify 40 microencapsulated odorants and his olfactory performance is compared with that of age- and sex-matched normal individuals. Unique features of this test are a means for detecting malingering and amenability to self-administration. Air-dilution olfactory detection is a more refined way of determining thresholds of sensation and of demonstrating normal olfactory perception in the absence of identification. Olfactory evoked potentials are being used in some electrophysiology laboratories, but their reliability is uncertain. These refined techniques are essentially research tools and are not used in neurologic practice.

The loss of smell usually falls into one of three categories: *nasal* (in which odorants do not reach the olfactory receptors), *olfactory neuroepithelial* (due to destruction of receptors or their axon filaments), and *central* (olfactory pathway lesions). In an analysis of 4000 cases of anosmia from specialized clinics, Hendriks found that three categories of pathology—nasal or paranasal sinus disease, viral infection of the upper respiratory tracts (the largest group), and head injury—accounted for most of the cases. Regarding the nasal diseases responsible for bilateral hyposmia or anosmia, the most frequent are those in which hypertrophy and hyperemia of the nasal mucosa prevent olfactory stimuli from reaching the receptor cells. Heavy smoking is said to be the most frequent cause of hyposmia. Chronic atrophic rhinitis; sinusitis of allergic, vasomotor, or infective types; nasal polyposis; and overuse of topical vasoconstrictors are other common causes. Biopsies of the olfactory mucosa in cases of allergic rhinitis have shown that the sensory epithelial cells are still present, but their cilia are deformed and shortened and are buried under other mucosal cells. Influenza, herpes simplex, and hepatitis virus infections may be followed by hyposmia or anosmia due to destruction of receptor cells, and, if the basal cells are also destroyed, this may be permanent. These cells may also be affected as a result of atrophic rhinitis and local radiation therapy or by a very rare type of tumor (*esthesioneuroblastoma*) that originates in the olfactory epithelium. There is also a group of rare diseases in which the primary receptor neurons are congenitally absent or hypoplastic and lack cilia. One of these is the Kallman syndrome of congenital anosmia and hypogonadotropic hypogonadism. A similar disorder occurs in the Turner syndrome and in albinos, because of the absence of “olfactory pigment” or some other congenital structural defect.

Anosmia that follows head injury is most often due to tearing of the delicate filaments of the receptor cells as they pass through the cribriform plate, especially if the injury is severe enough to cause fracture. The damage may be unilateral or bilateral. With closed head injury, anosmia is relatively infrequent (6 percent of Sumner's series of 584 cases).

Some recovery of olfaction occurs in about one-third of all head trauma cases over a period of several days to months. Beyond 6 to 12 months, recovery is negligible. Cranial surgery, subarachnoid hemorrhage, and chronic meningeal inflammation may have a similar effect. Strangely, in some of the cases of traumatic anosmia, there is also a loss of taste (ageusia). Ferrier, who first described traumatic ageusia in 1876, noted that there was always anosmia as well—an observation subsequently corroborated by Sumner. Often the ageusia clears within a few weeks. A bilateral lesion near the frontal operculum and paralimbic region, where olfactory and gustatory receptive zones are in close proximity, would best explain this concurrence. Obviously the interruption of olfactory filaments alone would not explain ageusia.

In women, olfactory acuity varies throughout the menstrual cycle and may be disordered during pregnancy. Nutritional and metabolic diseases such as thiamine deficiency, vitamin A deficiency, adrenal and perhaps thyroid insufficiency, cirrhosis, and chronic renal failure may give rise to transient anosmia, all as a

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result of sensorineural dysfunction. A large number of toxic agents—the more common ones being organic solvents (benzene), metals, dusts, cocaine, corticosteroids, methotrexate, aminoglycoside antibiotics, tetracyclines, opiates, and L-dopa—can damage the olfactory epithelium (Doty et al).

It has been reported that a large proportion of patients with degenerative disease of the brain show anosmia or hyposmia, for reasons that are quite unclear. Included in this group are Alzheimer, Parkinson, Huntington, and Pick disease and the Parkinson-dementia syndrome of Guam. The studies relating to this subject have been reviewed in detail by Doty. A number of theories have been proposed to explain these findings, but they are conjectural. It has been known for some time that alcoholics with Korsakoff psychosis have a defect in odor discrimination (Mair et al). In the latter disorder, anosmia is presumably due to degeneration of neurons in the higher-order olfactory systems involving the medial thalamic nuclei. Hyman and colleagues have remarked on the early neuronal degeneration in the region of the hippocampus in cases of Alzheimer disease, but we know of no studies of the central olfactory connections in this or any other degenerative disorder. Anosmia has been found in some patients with temporal lobe epilepsy and in some such patients who had been subjected to anterior temporal lobectomy. In these conditions, Andy and coworkers have found an impairment in discriminating the quality of odors and in matching odors with test objects seen or felt.

As with other sensory modalities, olfaction (and taste) are diminished with aging. The receptor cell population is depleted, and if the loss is regional, neuroepithelium is slowly replaced with respiratory epithelium (which is normally present in the nasal cavity and serves to filter, humidify, and warm incoming air). Neurons of the olfactory bulb may also be reduced as part of the aging process.

Bilateral anosmia is an increasingly common manifestation of *malingering*, now that it has been recognized as a compensable disability by insurance companies. The fact that true anosmics will complain inordinately of a loss of taste (but show normal taste sensation) may help to separate them from malingerers. Testing of olfactory evoked potentials, if

perfected, would be of use here.

The nasal epithelium or the olfactory nerves themselves may be affected in Wegener granulomatosis and by craniopharyngioma. A meningioma of the olfactory groove may implicate the olfactory bulb and tract and may extend posteriorly to involve the optic nerve, sometimes with optic atrophy; these abnormalities, if combined with papilledema on the opposite side, are known as The Foster Kennedy syndrome (page 260). A large aneurysm of the anterior cerebral or anterior communicating artery may produce a similar syndrome. With tumors confined to one side, the anosmia may be strictly unilateral, in which case it will not be reported by the patient but will be found on examination. Children with anterior meningoencephaloceles are usually anosmic and, in addition, may exhibit cerebrospinal fluid (CSF) rhinorrhea when the head is held in certain positions. Injury of the cribriform plate and hydrocephalus are other causes of CSF rhinorrhea. These defects in the sense of smell are attributable to lesions of either the receptor cells and their axons or the olfactory bulbs, and current test methods do not distinguish between lesions in these two localities. It is not known whether olfactory symptoms may be produced by lesions of the anterior perforated space or of the medial and lateral olfactory striae. In some cases of increased intracranial pressure, olfactory sense has been impaired without evidence of lesions in the olfactory bulbs.

The term *specific anosmia* has been applied to an unusual olfactory phenomenon, in which a person with normal olfactory acuity for most substances encounters a particular compound or class of compounds that is odorless to him, although obvious to others. In a sense, this is a condition of "smell blindness," analogous to color blindness. The basis of this disorder is unclear, although there is evidence that specific anosmia for musky and urinous odors is inherited as an autosomal recessive trait (see Amoore).

Whether a true *hyperosmia* exists is a matter of conjecture. Neurotic individuals may complain of being unduly sensitive to odors, but there is no proof of an actual change in their threshold of perception of odors. During migraine attacks and in some cases of aseptic meningitis, the patient may be unusually sensitive not only to light and sound but sometimes to odors as well.

## Dysosmia or Parosmia

These terms refer to distortions of odor perception, where an odor is present. Parosmia may occur with local nasopharyngeal conditions such as empyema of the nasal sinuses and ozena. In some instances the abnormal tissue itself may be the source of unpleasant odors; in others, where partial injuries of the olfactory bulbs have occurred, parosmia is in the nature of an olfactory illusion. Parosmia may also be a troublesome symptom in middle-aged and elderly persons with a depressive illness, who may report that every article of food has an extremely unpleasant odor

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(cacosmia). Sensations of disagreeable taste are often associated (cacogeusia). Nothing is known of the basis of this state; there is usually no loss of discriminative sensation.

The treatment of parosmia is difficult. The use of antipsychotic drugs has given unpredictable results. Claims for the efficacy of zinc and vitamins have not been verified.

Some reports indicate that repeated anesthetization of the nasal mucosa reduces or abolishes the parosmic disturbance. In many cases the disorder subsides spontaneously. Minor degrees of parosmia are not necessarily abnormal, for unpleasant odors have a way of lingering for several hours and of being reawakened by other olfactory stimuli (phantosmia), as every pathologist knows.

## Olfactory Hallucinations

These are always of central origin. The patient claims to smell an odor that no one else can detect (phantosmia). Most often this is due to temporal lobe seizures ("uncinate fits"), in which circumstances the olfactory hallucinations are brief and accompanied by an alteration of consciousness and other manifestations of epilepsy (page 339).

If the patient is convinced of the presence of a hallucination and also gives it personal reference, the symptom assumes the status of a delusion. The combination of olfactory hallucinations and delusions of this type signifies a psychiatric illness. Zilstorff has written informatively on this subject. There is often a complaint of a large array of odors, most of them foul. In most cases, the smells seem to emanate from the patient (intrinsic hallucinations); in others, they seem to come from an external source (extrinsic hallucinations). Both types vary in intensity and are remarkable with respect to their persistence. They may be combined with gustatory hallucinations. According to Pryse-Phillips, who took note of the psychiatric illness in a series of 137 patients with olfactory hallucinations, most were associated with endogenous depression and schizophrenia. In schizophrenia, the olfactory stimulus is usually interpreted as arising externally and as being induced by someone for the purpose of upsetting the patient. In depression, the stimulus is usually intrinsic and is more overwhelming. The patient uses all manner of ways to get rid of the perceived stench, the usual ones being excessive washing and use of deodorants; the condition may lead to social withdrawal. There is some reason to believe that the amygdaloid group of nuclei is the source of the hallucinations, since stereotactic lesions here have reportedly abolished both the olfactory hallucinations and the psychiatric disorder (Chitanondh).

Olfactory hallucinations and delusions may occur in conjunction with senile dementia, but when this happens one should also consider the possibility of an associated late-life depression. Occasionally olfactory hallucinations are part of an alcohol withdrawal syndrome. Peculiar reactions to smell characterize certain sexual psychopathies. Usually the stimuli appear to be extrinsic, but in this regard it should be noted that odors imagined by normal individuals are also perceived as coming from outside the person through inspired air, and unpleasant ones are more clearly represented than pleasant ones.

In lower vertebrates, these functions and similar ones (modulation of menstrual and reproductive behavior) have been attributed to the activities of a subset of olfactory receptors in the rostral end of the nasal mucosa. The axons of these cells penetrate the cribriform plate and synapse with secondary neurons in a discrete portion of the olfactory bulb (accessory olfactory bulb). This functionally and anatomically distinct olfactory tissue is referred to as the *vomeronasal system or organ of Jacobson* (see review of Wysocki and Meredith).

## Loss of Olfactory Discrimination (Olfactory Agnosia)

Finally, one must consider a disorder in which the primary perceptual aspects of olfaction (detection of odors, adaptation to odors, and recognition of different intensities of the same odor) are intact but the capacity to distinguish between odors and their recognition by quality is impaired or lost. In the writings on this subject, this deficit is usually referred to as a disorder of olfactory discrimination. In dealing with other sense modalities, however, the inability to identify and name a perceived sensation would be called an *agnosia*. To recognize this deficit requires special testing, such as matching to sample, the identification and naming of a variety of scents, and determining whether two odors are identical or different. Such an alteration of olfactory function has been shown to characterize patients with the alcoholic form of Korsakoff psychosis; this impairment is not attributable to impaired olfactory acuity or to failure of learning and memory (Mair et al). As indicated above, the olfactory disorder in the alcoholic Korsakoff patient is most likely due to lesions in the medial dorsal nucleus of the thalamus; several observations in animals indicate that this nucleus and its connections with the orbitofrontal cortex give rise to deficits in odor discrimination (Mair et al; Slotnick and Kaneko). Eichenbaum and associates demonstrated a similar impairment of olfactory capacities in a patient who had undergone extensive bilateral medial temporal lobe resections.

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The operation was believed to have eliminated a substantial portion of the olfactory afferents to the frontal cortex and thalamus, though there was no anatomic verification of this. In patients with stereotactic or surgical amygdalotomies, Andy and coworkers noted a similar reduction in odor discrimination. Thus it appears that both portions of the higher olfactory pathways (medial temporal lobes and medial dorsal nuclei) are necessary for the discrimination and identification of odors.

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