

Chapter 36: Physiology of Olfaction

Donald A. Leopold

The perception of odors adds a quality to life that is difficult to express. Odors are part of our everyday life, from the pleasures of perfume to the satisfaction of toast and coffee to the warnings of skunks and fire. As the molecules of substances are transported through the nose, the possibility of them being perceived occurs. The quality and intensity of that perception depends upon the anatomic state of the nasal epithelium and the status of the peripheral and central nervous systems.

This chapter explores the physiology of olfaction, noting pertinent research data. The initial discussion focuses on the pathways and obstacles that odorant molecules must negotiate as they come in contact with the olfactory receptor cells. A consideration of the neural processing of odorant stimulation and the pathways projecting to the brain gives some insight into the mechanisms underlying olfactory perception. Olfactory testing allows assessment of this perception, and methods to accomplish this are explored. The chapter ends with a section on clinical olfactory problems in humans and includes suggestions for their diagnosis and treatment.

The study of olfaction poses a number of tantalizing questions. For example: like many animal species, do humans communicate via odorant signals (pheromones)? Why are primary olfactory receptor cells able to regenerate entirely when other special sensory primary neurons are not? Research in this field has attracted the attention of researchers in the fields of endocrinology, anatomy, biochemistry, and neurophysiology, among others. Through these efforts, the ability to diagnose and help individuals with chemosensory problems is improving.

Anatomy of Olfactory Stimulation

Nasal passageways

Experiencing an odor is a result of input from the olfactory, trigeminal, glossopharyngeal, and vagus nerves. Apparently, properties of any given odorant determine the particular "mix" of these various inputs. Olfactory nerve (cranial nerve I) stimulation, which is necessary for identification of the vast majority of odorants, depends on the odorant molecules reaching the olfactory mucosa at the top of the nasal cavity. Although molecules can reach the olfactory cleft by diffusion, essentially all olfaction requires some type of nasal airflow. This airflow can even be the small amount of retronasal airflow generated by mouth and pharyngeal motion (Burdach and Doty, 1987; Mozell et al, 1986; Schwartz et al, 1987). Nasal models have shown this flow to be partially turbulent in the lower nose at lower flow rates (Girardin et al, 1983), and turbulent in most of the nasal cavity at higher flow rates (Hornung et al, 1987; Scherer et al, 1989). Additional data from a large-scale model (Fig. 36-1) indicate that at physiologic airflow rates, at least 50% of the total airflow passes through the middle and inferior meatuses, and about 15% flows through the olfactory region (Scherer et al, 1989). Using ink threads in a water flow medium through a model, Masing (1967) demonstrated that even the locus of entry through the

nostril can determine the path of that flow stream through the nose (Fig. 36-2).

The effect of a rapid change in flow velocity, such as with a sniff, on the *in vivo* airflow pattern remains unknown. Scherer et al (1989) have found in their large-scale model studies that the percentage and velocity of airflow to the olfactory region is similar for various steady-state airflow rates in the physiologic range. The fact remains, however, that sniffing is an almost universally performed maneuver when a person is presented with an olfactory stimulus. It is possible that its purpose is momentarily to increase the number of olfactory molecules in the olfactory cleft by a transient change in the airflow pattern of the nose. Sniffing duration, flow velocity, and volume are quite different among subjects but stay remarkably constant for any one subject (Laing, 1982). Furthermore, Laing (1983) has shown that different sniffing paradigms do not improve a subject's olfactory perception: the naturally chosen sniff seems to be optimal for that subject's nasal anatomy.

For molecules to reach the olfactory area, they must pass through the tall but narrow nasal passageways. The epithelium lining the walls of these passageways is wet, has variable thickness, and is aerodynamically "rough". Schneider and Wolf (1960) have observed that the best olfactory ability occurs when this epithelium is moderately congested, wet, and red, such as during an upper respiratory infection. Further, olfactory ability appears to improve with narrowed nasal chambers (Doty, 1979; Youngentob et al, 1982), but the changes in nasal patency that occur during the natural rhythmic engorgement and thinning of the nasal epithelium (nasal cycle) (Principato and Ozenberger, 1970) do not have any effect on olfactory ability (Doty and Frye, 1989; Eccles et al, 1989; Leopold et al, unpublished data).

The sorption of molecules to these mucus-lined walls extracts some of them from the air stream and increases their travel time. This process could preferentially influence the spectrum of chemicals reaching the olfactory cleft or could at least spread their arrival over time. Moncrieff (1955) described this phenomenon in the variable times required for odorants to traverse the nasal passageways of sheep. This sorption of molecules may act to separate or sort the odorants before they react the olfactory mucosa. Highly sorbable chemicals may have little or no odor simply because they sorb to the nasal walls before they reach the olfactory cleft, thereby accentuating the trigeminal component. Could it be that our world would smell different if we had no external nose to increase the path of the olfactory region? Does an animal with a long snout, such as the dog, smell the world differently as a result of these sorptive effects?

Olfactory mucus

After the odorant molecules reach the olfactory region, they must interact with the mucus overlying the receptor cells. The mucus apparently comes from both Bowman's glands deep in the lamina propria (only of serous type in humans) (Graziadei, 1971; Jafek, 1983) and the adjacent respiratory mucosa (goblet cells). Researchers have observed that the supporting (sustentacular) cells of the human olfactory epithelium are not histologically equipped to secrete mucus (Jafek, 1983; Moran et al, 1982a, 1982b). The supporting cells of most other species, however, have been shown to secrete mucus, often in response to odorants (Getchell and

Getchell, 1977a, 1977b; Graziadei, 1971; Okano and Takagi, 1974).

The partitioning of an odorant's molecules between the air phase and the mucus phase is most certainly another determinate of its being perceived. To reach the olfactory receptors, the odorant molecules must be soluble in the mucus but, as Laffort et al (1974) argue, not so "strongly captured" that they are unable to interact with the receptors. In addition, changes in the thickness or composition of the mucus can influence the diffusion time required for odorant molecules to reach the receptor sites (Getchell et al, 1984). Beta-adrenergic, cholinergic, and peptidergic agents have caused these changes in the mucus overlying the olfactory receptors through their effect on the secretory activities of the mucosal glands. Moreover, these same agents have been shown to influence the sensitivity of the olfactory receptor cells themselves (Bouvet et al, 1988; Getchell and Getchell, 1990; Getchell et al, 1988).

Once in the olfactory mucus-epithelial system, the rate at which the odorant is cleared is also important. Hornung and Mozell (1981) have shown that 78% of a radioactively labeled odorant (butanol) remained trapped in the mucus 30 minutes after inspiratory exposure, whereas radioactively labeled octane cleared very rapidly. The mucus may exert a differential role in deactivating, removing, or desorbing odorants from the olfactory area.

Olfactory epithelium

Located 7 cm inside the nasal cavity, the olfactory sensory neurons are protected in a 1-mm wide crevice of the posterosuperior nose. At the epithelial surface, these bipolar neurons are exposed to the outside world via their dendrites and cilia. Proximally, axons of these same neurons synapse at the base of the brain (olfactory bulb). Whereas the olfactory receptor region is a solid sheet of olfactory mucosa in human fetuses and laboratory animals housed in a protected environment, Morrison and Costanzo (1990), Naessen (1971), and Nakashima et al (1984) have shown that there is mixing of olfactory and respiratory epithelial tissues in adults humans (Fig. 36-3). The number of these clumps of respiratory epithelium, which are found in the olfactory area, may increase with age, suggesting that a loss of primary olfactory neurons at least partially explains the decreased olfactory ability associated with aging.

The human olfactory epithelium is much thicker (60-70 microm) than the surrounding respiratory epithelium (20-30 microm) and covers an area of roughly 1 sq cm on each side. The epithelium is pseudostratified columnar, and it rests on a vascular lamina propria with no submucosa (Fig. 36-4). In most mammals studied, four main cell types have been identified (Figs. 36-5 and 36-6): ciliated olfactory receptors, microvillar cells, supporting (sustentacular) cells, and basal cells (Moran et al, 1982a, 1982b; Morrison and Costanzo, 1990; Rowley et al, 1989). Ongoing research using immunohistochemical staining of olfactory elements continues to provide information on growth, maturation, function of specific cellular elements, and similarities with other neural tissue (Carr et al, 1989; Schwob, 1991; Schwob et al, 1986; Verhaagen et al, 1990; Yamagishi et al, 1989b, 1989c). One possible use for this technique may be to clarify the etiology of the patient's olfactory dysfunction and possibly offer a prognosis regarding improvement of olfactory ability (Leopold et al, unpublished data; Yamagishi et al, 1990).

The olfactory receptor neuron is bipolar and has a club-shaped peripheral "knob" that bears the cilia (Fig. 36-7). After widening for the nucleus, it tapers to the long, thin, nonmyelinated axon that can travel several centimeters to the olfactory bulb. Bundles of these fibers form in the lamina propria and become ensheathed as a group by the plasma membranes of the Schwann cells, forming the olfactory nerve (cranial nerve I), which traverses the 15 to 20 foramina in the cribriform plate to synapse in the bulb. Allison and Warwick (1949) estimate the rabbit to have about 50 million olfactory axons, whereas Jafek (1983) estimates humans to have only 6 millions bilaterally.

The microvillar cell occurs about one tenth as often as the ciliated olfactory neurons (Jafek, 1983). The cell body is flask shaped and located near the epithelial surface, and has an apical membrane containing microvilli that project into the mucus overlying the epithelium (Fig. 36-6) (Moran et al, 1982a, 1982b). The deep end of the cell tapers to a thin, axonlike cytoplasmic projection that proceeds into the lamina propria. Although there is no electrophysiologic evidence that these cells respond to chemical stimuli, Rowley et al (1989) have hypothesized that they are a "morphologically distinct class of sensory receptor". Their evidence for this is the backfilling of a cytochemical tracer macromolecule (horseradish peroxidase) into the ciliated olfactory receptors *and* the microvillar cells when it is injected into the olfactory bulb.

Situated among these two receptor type cells are the supporting, or sustentacular, cells. These tall cells have an apical membrane that joins tightly with the surface of the receptor cells and the microvillar cells. They seem positioned to separate the receptor cells from each other; however, intimate apposition between receptor cells does occur (Jafek, 1983; Moran et al, 1982a, 1982b). Whether this proximity allows some receptor cells to influence each other's firing patterns is unknown. Sustentacular cells do not generate action potentials, nor are they electrically coupled to each other (Getchell, 1977; Masukawa et al, 1985); thus they do not seem to contribute directly to the olfactory transduction process and the elicitation of generator potentials by odorant stimuli.

Deep to these cells, the basal cells sit along the lamina propria. They serve as a stem cell population that can differentiate to replace the olfactory receptors lost during cell turnover or as a consequence of environmental insult (Jafek, 1983). This renewal of a special sensory neuron, as demonstrated by Graziadei (1973), is not known to occur in other sensory systems. The replication cycle is between 3 and 7 weeks (Monti-Graziadei and Graziadei, 1979; Moulton and Beidler, 1967). When the new receptor cell forms, it also projects its axon to the olfactory bulb where it synapses.

The surface of human olfactory epithelium is covered with cilia, but electron-microscopic studies reveal no dynein arms on these cilia (Jafek, 1983; Moran et al, 1982b). These authors conclude from this observation that neither dynein arms nor motility is essential for human olfaction. In other animals, cilia can be differentiated on the basis of their length, motility, and response to odorant stimuli (Adamek et al, 1981; Gesteland et al, 1982; Mair et al, 1980, 1982). Different patterns of ciliary movement are a function of age and development. In the immature neuron the cilia move rapidly and randomly, and the cell responds electrophysiologically to a large

number of chemical stimuli. After the cell has made a central connection with the olfactory bulb, this more mature neuron exhibits longer, slower cilia motion and responds more selectively to odorants. The most mature neurons have immotile cilia.

Olfactory bulb

The olfactory bulb (Fig. 36-8) lies at the base of the frontal cortex in the anterior fossa. It serves as the first relay station in the olfactory pathway, where the primary olfactory neurons synapse with secondary neurons. These synapses and their postsynaptic partners form dense aggregates of neuropil called glomeruli. In the adult rabbit, approximately 26,000 olfactory axons enter each glomerulus, where they contact roughly 100 second-order neurons (Allison, 1953). This relationship indicates a considerable convergence of information as these neurons pass from the periphery onto this first central station. (The interconnection among the various glomeruli in one bulb, the interconnections between bulbs, and the afferent and efferent connections with the brain indicate that considerable processing also occurs at the bulb level.)

The neuronal projection of the olfactory mucosa onto the bulb displays some anatomic restrictions but is not strictly point to point. In other words, a given region of the bulb receives its densest input from a particular region of the mucosa (Pedersen et al, 1986), but inputs to a particular region of the bulb converge from many areas along the anteroposterior extent of the mucosa. Conversely, a small focus in the epithelium will project widely, but within a restrictive region of the bulb (Kauer, 1991). These dense and diffuse inputs possibly represent excitatory and inhibitory influences, which, as in other sensory systems, narrow the neural stimulus representation as the processing moves centrally. Alternatively, the convergence and divergence of projections from neurons in the epithelium may serve to coalesce inputs from receptor cells of like sensitivity to odorants. Evidence to support this notion emerges from the coherent activation of single glomeruli or sets of glomeruli by specified odorants (Jourdan et al, 1980; Stewart et al, 1979). Thus, it is clear that the microcircuitry of the bulb is specialized to narrow the spatial pattern of the glomerular activation elicited by an odorant or mixture of odorants.

Olfactory connections in brain

Although the neural connections from the olfactory mucosa to the olfactory bulb are spatially organized to an extent, there is no spatial organization of the olfactory bulb output to the olfactory cortex (Macrides et al, 1985; Scott, 1986). Although complex neural branching and small fiber size have made anatomic mapping and electrical recording of specific nerve fiber tracts difficult, studies of neural function are making it clear that there may be physiologic differences among the mitral and tufted cell classes (Scott, 1987). The more central olfactory connections include the olfactory tubercle, the prepyriform cortex, part of the amygdaloid nuclei, and the nucleus of the terminal stria with further projections to a number of structures, including the hypothalamus. Although these structures receive olfactory input, they also serve other functions such as food intake, temperature regulation, sleeping cycles, vision, hearing, and taste. It is also possible that these structures influence the olfactory process by efferent connections (Engen, 1982).

Common clinical sense

Free nerve endings of three cranial nerves (trigeminal, glossopharyngeal, and vagus) provide added chemoreceptivity in the mucosa of the respiratory tract, the trigeminal being the most important (Cain, 1981; Cain and Murphy, 1980). They sense the "burn" of ammonia and the "bite" of hot pepper. In the nose, virtually all odorants stimulate both olfactory and trigeminal nerves to some degree, even when no apparent pungency can be perceived. The peripheral anatomic pathways for these cranial nerves have long been known; however, the central connections that allow their interaction and how they interrelate to other senses are just beginning to be determined (Cain, 1981; Laing, 1980; Murphy et al, 1977). Cometto-Muniz and Cain (1984) have shown that when tested with ammonia, the common chemical sense behaves more like a total mass detector than a concentration detector (ie, at a given concentration the perceived magnitude increases with the time of presentation). It is even possible that the trigeminal nerve interprets pungent or chemically irritative stimuli as being painful or nociceptive in nature.

Olfactory Transduction and Coding

At each level of the olfactory system different factors control or shape how the system works. The nose has narrow passageways lined by wet mucus and swept by alternating air currents. The hydrophilic olfactory mucus presents the incoming odorant molecules with constraints of sorption, solubility, and chemical reactivity. Once the odorant molecule is dissolved in the olfactory mucus, another group of events influences whether it can interact with the olfactory receptor cell(s). Soluble binding proteins, like odorant binding protein (OBP), have been described in air-breathing vertebrates, and it has been suggested that these proteins enhance the access of odorants to the olfactory receptors (Bignetti et al, 1985; Pevsner et al, 1986, 1988; Snyder et al, 1989). This is accomplished by binding and solubilizing hydrophobic odorant molecules, thus increasing their concentration in the environment of the receptor cell by as much as 1000 to 10,000 times more than their concentration in the ambient air (Senf et al, 1980). Additionally, these same OBP molecules may act to remove odorant molecules from the region of the receptor cell after transduction. It is also possible that air-breathing vertebrates may have in their olfactory systems a chemical sensing system like that of unicellular and multicellular organisms. This system can produce degradative products that transform stimulants into inactive products and vice versa (Carr et al, 1990). Thus there are many "perireceptor" events occurring in the olfactory mucus before the odorant actually comes into contact with the cilia of the olfactory receptor cell.

It is generally accepted that the actual transformation of odorant chemical information into an electrical action potential occurs as a result of specific interactions between odorant molecules and receptor proteins on the surface of olfactory cilia (Anholt, 1987; Getchell, 1986; Lancet, 1986, 1987; Lancet and Pace, 1987). This process is probably mediated by a G protein-coupled cascade using cyclic AMP as an intracellular second messenger. Clinical evidence supporting this comes from patients with type 1a pseudohypoparathyroidism, who not only have a deficiency in stimulatory G proteins but also have olfactory losses (Ikeda et al, 1988; Weinstock et al, 1986; Wright, 1991). This G protein, termed G_{olf} , appears to be exclusively localized to the olfactory

epithelium (Jones and Reed, 1989). The cyclic AMP appears to be involved in the olfactory process by directly influencing an ion channel in the olfactory cilia (Dhallan et al, 1990; Nakamura and Gold, 1987). In the evolving model for this transduction, the odorant stimulates an increase in the intracellular cyclic AMP concentration, which in turn activates the ion channel and depolarizes the sensory neuron. (An analogous cascade through a similar channel mediates visual transduction in photoreceptor cells, suggesting that the two systems may use homologous channels.) Whether calcium is involved in this transduction is unclear at this time, but it may be that the odorant-induced influx of calcium initiates the series of events as outlined above (Anholt, 1989).

Once the peripheral olfactory receptor cells are depolarized, there begins a convergence of electrical information towards the olfactory bulb. How that information is coded for the thousands of odorants that can be recognized and discriminated is still unknown; however, Adrian (1950a, 1950b, 1951, 1953a, 1953b, 1954) has suggested several mechanisms based on his electrophysiologic recordings. Taken together, all these mechanisms could produce different activity patterns across the mucosa, which would explain the different activity patterns he observed from anterior and posterior locations in the bulb. One mechanism is the odorant-selective sensitivity of the individual receptors, such that incoming odorants would excite different patterns of receptors along the mucosal surface. A second mechanism extends this concept, suggesting that receptors of like sensitivity will be aggregated into particular regions of the mucosa, thus giving a different spatial representation for each odorant. The final mechanism Adrian suggests proposes that each odorant, having different physicochemical properties such as solubility, would spread differentially both in time and space across the mucosal sheet. Adrian's proposals have been supported by later investigators.

The selective sensitivity of the receptor cells, Adrian's first mechanism, was clinically suspected by the existence of individuals with specific reduced sensitivity to certain odorants (Amoore, 1971, 1977). Electrical recordings from single receptor cells in the olfactory mucosa in animals demonstrate that each cell is "tuned" to different groups of chemicals; no cell responds to all odorants. However, it is difficult to classify these cells into particular types because no two cells respond to the same total group of odorants (Gesteland et al, 1965; Mathews, 1972). By studying the electrical responses of 30 receptor cells in the spiny lobster, Girardot and Derby (1990) have suggested that the quality part of olfactory coding is determined by the pattern of the response across the neuronal population and the intensity by the absolute magnitude. This would allow the lobster to determine whether the incoming odorant is from friend or foe (quality) and how close he is (intensity).

Several investigators have observed, as Adrian suggested, that receptor cells of like selectivity might indeed be aggregated into particular regions of the mucosa (Kauer and Moulton, 1974; Kubie and Moulton, 1979; Kubie et al, 1980; Mackay-Sim and Kubie, 1981; Mackay-Sim and Moulton, 1980; Mackay-Sim et al, 1982; Moulton, 1976). After surgically exposing the salamander's olfactory mucosa, the investigators puffed odorants directly onto the different regions while recording the electrical activity. Different regions gave maximal responses to different odorants.

Mozell (1964b, 1966, 1970) has analyzed the concept of spatial and temporal activity patterns. By electrically sampling olfactory nerve branches receiving input from the regions near the external and internal nares of the bullfrog, Mozell found each odorant produced a characteristic gradient of activity. The time interval between the responses at the external and internal nares was also measured and was found to correlate with the activity gradients. This fit in well with Adrian's theory because the molecules of different odorants spread differently across the mucosa both in time and space. Later experiments, including the use of radioactive odorants, suggest that these spatiotemporal patterns result from the differential sorption of the molecules of different odorants across the mucosal sheet (Hornung and Mozell, 1977; Laing, 1987; Mozell, 1964a; Mozell and Jagodowicz, 1973, 1974). Furthermore, spatiotemporal patterns have also been demonstrated in the olfactory bulb (Wilson and Leon, 1988), and they can be modified by early learning. It is becoming apparent that there is a great deal of learning in the early postnatal time period to establish these patterns.

The contribution made by the central nervous system towards olfactory coding and discrimination is unclear. It may be that the olfactory code is complete by the time it leaves the olfactory bulb. Alternatively, the code may need to be completed by additional central neural processing. Whatever the status of the olfactory code, it is clear that the central nervous system uses olfactory information for many purposes. One such purpose, for instance, is in the area of feeding. Glucose-sensitive cells in the lateral hypothalamus of the monkey integrate many chemosensory inputs from both endogenous and exogenous sources, whereas glucose-insensitive cells from the same area distinguish among fewer, more specific chemosensory cues to control food acquisition behavior (Karadi et al, 1989).

Where the central nervous system processes the olfactory information is also unclear. Studies on laterality have suggested that humans have a "better" side for olfactory ability (Hornung et al, 1990; Youngentob et al, 1982). Zatorre and Jones-Gotman (1990) have even suggested that the right side is the better one, based on their observation of no deficits in olfactory identification ability in patients after left central, parietal, and posterior brain excisions. This is supported by the finding that patients with right parietal and frontotemporal lesions have difficulty with the lateralization of odorants (Bellas et al, 1989). Handedness may be a determinant of this trend (Koelega, 1979), or the preferred side may be related to learning.

Olfactory Cognition

Odors are understood largely on the basis of experience, and each individual develops his own hedonic code within cultural restraints (Ellis, 1982; Hvastja and Zanuttini, 1989; Lindvall et al, 1973). Odor association, once established, are notoriously difficult to erase from memory (Engen, 1982; Wippich et al, 1989), even though the incident that formed the association is forgotten or seems irrational. In one study, odor memory was shown to last at least a year, whereas visual memory lasted only a few months (Engen, 1982) (Fig. 36-9). An odor aversion can be formed to a perfectly good food by overindulgence. Similarly, becoming ill for another reason while eating otherwise innocuous food can have the same effect (Engen, 1982). This same phenomenon is used effectively in animal training, when lithium chloride, an emetic, is given

with food in order to induce an aversion.

Whether or not newborn human babies discriminate between pleasant and unpleasant odors or whether the sense of smell enters into their enjoyment of food is debatable (Engen, 1982). They can, however, identify odorants having biologic meaning. Macfarlane (1975) has shown that, by the age of 6 to 10 days, infants prefer a pad from their own mother's breast as opposed to one from a strange mother. Other studies have shown that between the ages of 3 and 5 years, odor perception plays a role in a child's attachment to his mother (Schall et al, 1980). Somewhere between the ages of 2 and 7 years, children start to show odor preferences, and these are similar to those of the adults living in the same area (Engen, 1974; Schmidt and Beauchamp, 1988; Strickland et al, 1988). All these observations of early human olfactory development have parallels in other mammals. Several researchers have suggested that this development is related to the marked growth that occurs in the neural circuitry of the olfactory epithelium and olfactory bulb from birth until adult size is reached (Meisami, 1989; Pomeroy et al, 1990). Pheromones, which are pervasive throughout the subhuman animal kingdom, are chemicals released by one member of a species and received by another member, resulting in a specific action or developmental process (Karlson and Lüscher, 1959). Thus, the male hamster knows whether the female is receptive (Devoir and Chorover, 1975; Murphy, 1973), and the ant knows the trail laid by a conspecific to a particular food (Cavill and Robertson, 1965). (A more complex listing of messages that are probably conveyed among mammals by means of olfaction is in the box (Doty, 1986; Mykytowycz, 1970)). The search for a human pheromone has been going on for many years, and various "biologic" odorants refined from human urine, axillary secretions, and vaginal secretions have been touted, often in the popular press, as being pheromones. Both anatomic and behavioral studies support the possibility of human communication via odorants; however, additional studies using double-blind techniques are needed before adequate conclusions can be made (Doty, 1977; Doty et al, 1975, 1979, 1981). One example of the type of human biologic activity on which olfactory control can be exerted is menstrual cycle synchrony. Russell et al (1980) placed a mixture of alcohol and underarm secretion from one woman on the upper-lip skin of five women subjects and alcohol only on six control women subjects. Over a period of 5 months there was a statistically significant ($p < 0.01$) tendency for menstrual synchrony with the woman who donated the axillary secretions for the experimental group as compared with the control group. Although this study has some methodological problems (Doty et al, 1981), it highlights the olfactory communication that may be going on among humans.

Stimulation and Measurement of Olfaction

For many years, the clinical evaluation of olfactory ability was simply to determine whether the patient could detect any odorant at all. However, just as this type of "yes-or-no" testing is no longer acceptable in the evaluation of vision or hearing, it is also not acceptable for olfactory evaluation. Careful clinical practice demands quantitative, repeatable tests that can be used to document olfactory ability during the course of a medical treatment or across time. The two aspects of olfaction most commonly tested are threshold and identification ability. Of these, identification is the most related to everyday olfactory functioning.

Box. Types of messages conveyed by mammals by means of olfaction

Age appraisal	Individual appraisal
Alarm	Pain indication
Attention-seeking	Predator
Defense	Prey
Distress-signalling	Reproductive stage indication
Frustration	Social status appraisal
Gender appraisal	Species membership
Greeting	Gender appraisal
Gregariousness	Submission
Group membership appraisal	Territory marking
Identification with home range	Trail marking
	Warning.

The measurement of the detection threshold attempts to quantify the most dilute concentration of a particular odorant that an individual can detect. Stuver (1958) estimated that the number of molecules needed to excite a single receptor is at most nine, and perhaps as few as one for mercaptans (skunk-like odorants). Stuver further estimated that at least 40 receptors must be excited to reach the threshold level. The general format of this test is to use a series of bottles containing a range of concentrations in predetermined steps. Although pyridine and n-butyl alcohol (1-butanol) are two of the most widely used test chemicals because of their water solubility, easy identifiability, and history of successful use, phenyl ethyl alcohol, which has a rose-like smell, may be a better choice because it has less trigeminal reactivity (Doty et al, 1978). The odorants are presented from lowest to highest concentration until the subject correctly identifies four odorants at a given concentration. This order of presentation avoids the adaptation (ie, the loss of sensitivity from mere stimulation) that might occur if strong concentrations were to be used first (Cain, 1989). In the test situation, the subject is presented with two bottles, one containing the odorant and the other a blank. The subject is asked to choose the bottle that contains the odorant (two-alternative, forced-choice procedure) (Cornsweet, 1962; Levitt, 1971). Discretion should be used, however, in the interpretation of olfactory detection threshold scores, because the test-retest reliability of this test has been reported to be low (Heywood and Costanzo, 1986; Punter, 1983).

Identification tests allow the subject to smell a number of odorants and name them correctly. The test is a suprathreshold test; that is, the stimuli are presented at a concentration above threshold that the subject considers "normal" for that odorant. Additionally, identification tests presume normal cognitive ability. Without this ability, a low olfactory test score may be due to poor testing in someone with normal olfactory ability. Several versions of this test are available and commonly used. Cain et al (1983) have developed an identification test that is administered along with a threshold test. In this test, eight common household items (eg, baby powder, coffee, Ivory soap, etc) are presented to the subject in screw-top jars. The subject is graded on how many of the odorants he can identify correctly.

Doty et al (1984a, 1984b) have developed a method of testing identification ability using scratch-and-sniff booklets containing 40 microencapsulated odorants. This commercially available test is self-administered and can either be mailed to test subjects or used during the examination. Material accompanying the booklets allows percentile score ranking of test results by age and sex, which are known determinants of olfactory ability (see next section). Because the subject is asked to choose the correct answer from a list of four possible answers, a change performance would be 25% correct. Obviously, anyone scoring much less than this should be considered for malingering. The portability of the booklets, the freshness of the stimulus, and the fun of doing the test weight in its favor and contribute to its popularity.

Another use of an identification test is to better characterize the olfactory status of the patient with an olfactory complaint. Wright (1987) has applied a powerful psychophysical tool, the confusion matrix, to this task. In the Odorant Confusion Matrix (OCM), ten single chemical odorants representing common household items (eg, orange, vanilla, ammonia, etc) and one blank are presented to the subject in random order. The subject has a list of the ten odorants, and must choose one of the words for each presentation (forced-choice). This same sequence is then repeated nine more times, such that the group of odorants is administered ten times. The results can then be represented on a matrix, as in Fig. 36-10. Not only can the total and individual odorant percent correct scores be calculated from the diagonal, but trends showing improvement or decrement (fatigue or adapting) during the test can also be calculated. In analyzing the off-diagonal responses, the tendency for "clumping", or consistently responding with the same wrong answer can be determined. The ten odorants contain four that have varying degrees of pungency. Often an individual who has little or no cranial nerve I olfactory ability will be able to recognize these trigeminal stimulators, and this test can measure that effect.

In other parts of the world olfactory testing is also being performed, sometimes with one of the tests noted above, and sometimes with locally designed tests. In Japan, the standard test is the "T and T olfactometer", which is a rack containing eight concentrations of five different odorants. From this test, both detection and recognition thresholds can be determined, and they are charted on a graph similar to an audiogram (Tagagi, 1987). Hendriks and his colleagues (Hendriks, 1988) have developed a Dutch odor identification test (GITU - Geur Identificatie Test Utrecht) that has two subsets of 18 odorants each. This test has applicability for both clinical and industrial testing, and has proven useful in assessing the olfactory ability of adults in the Netherlands.

For all these olfactory tests, especially those measuring threshold, control of stimulus concentration is obviously important. In general, the two main techniques to control or vary odorant concentration are: (1) dilution of the liquid-phase odorant in varying amounts of solvent, and (2) dilution of the vapor-phase odorant with air. Racks of sniff bottles can be designed with a gradient of concentrations. Although they are conveniently portable, the liquids can become contaminated by oxidation, or the odorant concentration can be changed by oxidation or evaporation (Haring, 1974). Therefore, when open-bottle tests are used, the solutions must be changed frequently. More precise control over the stimulus intensity has been achieved with a variety of olfactometers. By mixing pure air and odorized air streams, the odorant concentrations

reaching the nose can be precisely controlled. Although these olfactometers are quite accurate in the control of the stimulus, their cost and size have restricted their use to research laboratories. Another variable in olfactory testing is the presentation of the odorant to the olfactory receptors. Although most techniques use the normal sniffing generated by the subject, some testing is done by puffing or blasting the odorant into the nose. These techniques should be avoided because the subject can confuse the somesthetic sensation of the blast with the odorant stimulus (Benignus and Prah, 1980; Jones, 1955). Normal sniffing is by far the easiest and most practical method, and according to Laing (1983), provides optimal perception. Moreover, he has found that the first sniff provides the most significant information, and that subsequent sniffs are simply confirmatory. Optimal sniff durations of 0.39 to 0.64 seconds have been noted for cranial nerve I-type odorants such as phenyl ethyl alcohol (rose) and propionic acid, whereas butanol, which has more trigeminal or "throat" sensation, requires a sniff lasting 1.63 seconds (Laing, 1985). It has also been shown that although there are wide differences among individuals in sniffing technique, they consistently maintain a unique sniff pattern (Laing, 1982). For these reason most clinical olfactory testing is done using a natural sniffing technique.

In an attempt to circumvent the problems of the air stream-delivered stimulus, the Japanese have included intravenous smell testing into their olfactory evaluation (Furukawa et al, 1988a). In this test, the subject is asked to perceive the mercaptan (garlic) smell of injected alinamin, a thiol-type derivative of vitamin B₁. The time between the injection and the recognition of the smell is designated as the *latent time*, and the time between the recognition and the disappearance of the smell is the *duration time*. They report that the latent time is influenced by olfactory acuity and that the duration time depends on adaptation to the odorant. Central olfactory disorders are suspected in patients with decreased duration times, and nonresponders to this test are said to have a poor prognosis of olfactory recovery. Although it is tantalizing to speculate that this intravenous test directly stimulates the olfactory receptor cells through the blood stream, studies by Okabe (1989) indicate that the mechanism of this test is by the discharge of alinamin's metabolic byproducts from the bloodstream into the pulmonary alveoli, from where it reaches the olfactory receptors through the nasopharynx via the exhaled air stream.

A problem often encountered in testing olfactory sensitivity is that many patients confuse the loss of the sense of smell with the loss of the sense of taste. Westerman (1981) has developed a simple test for such an evaluation whereby the odorant is placed on the tongue and the subject is asked to describe the flavor of the material. This test may also be used to identify malingerers because few individuals know that flavor is largely mediated through the sense of olfaction. When asked, therefore, to identify the "taste" of the coffee placed on his tongue, the blindfolded olfactory malingerer, who should report a "bitter" taste, will identify its taste as "coffee", but will disclaim any ability to identify the coffee odor when it is held in front of his nose.

Physiologic testing of olfactory ability in humans is being developed but at present is only a research tool. One of these tools, the electro-olfactogram (EOG), is obtained by placing an electrode directly on the olfactory epithelium. When an odorant stimulates the receptor cells, a slow negative shift in voltage is seen. This has been demonstrated in multiple animals, including

humans, and is thought to represent a summation of the many generator potentials from single receptor cells (Getchell, 1977; Okano and Takagi, 1974; Ottoson, 1956; Shibuya, 1964). Although the olfactory epithelium is relatively inaccessible in the human, some researchers, including Furukawa et al (1989), have succeeded in recording these EOG potentials and have demonstrated decreased potentials in hyposmics that are commensurate with their loss. As these researchers have said, the EOG provides the only objective method presently available for the differential diagnosis of anosmia caused by disorders of the olfactory epithelium versus the central olfactory tract.

A second objective testing method, used with success in other sensory systems such as hearing and vision, is measurement of brain-evoked potentials. In this test, the summated percutaneous brain electrical activity is averaged after multiple exposures to an odorant. Using this test in their research center, Kobal and Hummel (1988) have succeeded in determining when the olfactory stimulation arrives at the receptors and have shown differences between pure olfactory and trigeminal stimulation. It also has been reported that, with intact olfactory and trigeminal function, there are two olfactory evoked potentials, one at about 150 msec and the other at approximately 350 msec (Westhofen and Herberhold, 1987). As studies like these are expanded, objective testing will one day be available for clinical use.

A third objective method of testing olfactory ability uses computer technology for an on-line analysis of electroencephalographic (EEG) data. This brain electrical activity mapping (BEAM) technique can display colored topographic maps of the cortical activity while events, such as sniffing, are occurring (Duffy et al, 1984). This technique does not involve averaging of multiple trials (as does the evoked potential technique) and thus can display an individual response to a particular odorant. BEAM technology, which has already found use as a clinical tool in the diagnosis of dyslexia (Duffy and McAulity, 1985), can illustrate different responses to various odorants and promises to be useful in clinical olfactory evaluations (VanToller, 1988).

Factors Affecting Olfactory Testing

Age

The testing of olfactory ability in children presents special problems. Richman et al (1983, 1988), using an identification test designed for adults, found no consistent results in testing children under the age of 10, but by the age of 14 the children's performance was equal to that of adults. By using pictures to represent the odorants instead of words, reliable results could be obtained from children as young as age 6 (Richman, 1991). The children who had cleft lip and/or palate (CLP) generally did more poorly than did normal children of the same age. Boys in the CLP group were especially poor at olfactory identification. This suggests that there may be a sex bias in olfactory development or ability of children with CLP disorders. The other popular method for testing olfactory ability in adults, the detection threshold method, has been used in 5- to 15-year-old children using a forced-choice single-staircase method (Ghorbanian et al, 1983), but the clinical relevance of this, especially in children, is unclear. Engen (1982) found it very difficult to test a hedonic preference in children younger than 4 years of age. They answered

"yes" to his query regardless of whether the question was phrased positively or negatively (ie, both "Do you like it?" and "Do you dislike it?" yielded affirmative answers). More recent studies that used happy and sad faces or puppets have yielded more consistent results (Schmidt and Beauchamp, 1988; Strickland et al, 1988).

Testing older adults is generally only a problem if there has been a major loss of olfactory function, or if the patient has dementia. For individuals with very poor olfactory ability, the testing can be very boring, disheartening, and frustrating, all of which can lead to inadequate measurement of real olfactory ability. In testing olfactory ability in the demented individual, the tests used in children have been useful. Obviously, if someone is severely demented, any type of interactive testing will be futile.

Instruction

Dual thresholds exist in olfaction - one for recognition and another for identification (Tagagi, 1987). Engen (1960) demonstrated this dual threshold by asking subjects to either detect which one of four test tubes smelled different or to identify the one test tube out of the four that contained a specific odorant. The first set of instructions consistently yielded lower absolute thresholds. The fact that two thresholds seem to be acting in olfaction could indicate the presence of different receptor types, similar to the rods and cones of the retina, on the other hand, it could also mean that a certain level of summation of peripheral events is necessary at a central locus before positive identification can be made (Mozell, 1971).

Satiety

Because eating is so intimately associated with aromas, one might expect the prandial state of an individual to affect the sense of smell. The testing of olfactory ability in this situation can be influenced by the pleasantness of the odor. One must be careful to focus the subject on either the detection task or the hedonic judgement because one may affect the other (Engen, 1982). Cabanac (1971) has shown that hunger affects judgements of pleasantness with food odorants, but not psychophysical assessments of intensity. In general, a food odor is pleasant when one is hungry and less pleasant after one has overindulged in the food. By contrast, nonfood odorants, such as laboratory chemicals, generally do not show shifts in preference judgment (Mower et al, 1977).

Sex

In humans, test results have consistently shown that females have a better olfactory ability than males, both in threshold and in identification tasks (Velle, 1987). In addition, the menstrual cycle influences their olfaction threshold level, being best at ovulation and poorest during menstruation (Doty, 1977; Doty et al, 1981; Schneider, 1974). The reasons for this are not simply hormonal variations because Doty et al (1981) have shown olfactory cycling even in women using oral contraceptives, whose hormone levels did not vary. In animals a clear relation exists between olfaction and sexual functioning. Pregnancy in mice can be blocked by the odor of a

strange male (Bruce, 1960).

Adaptation and habituation

The perception of the strong odor noticeable upon entering a barn will disappear after a period of time. This adaptation response in humans, as measured by Stuiver (1958), generally occurred within 1 to 5 minutes for the chemicals studied. Data suggest that adaptation occurs both at the receptor cell level (Baylin and Moulton, 1979; Ottoson, 1956) and more centrally (Beidler, 1957; Koster, 1971; Stuiver, 1958). Central adaptation is supported by the finding that, in humans, continued stimulation through one nostril leads to adaptation in both nostrils (Stuiver, 1958).

Olfactory cross-adaptation is the ability of one chemical to decrease the subject's responsiveness and sensitivity to another chemical. It has been proposed that the greater the cross-adapting effect on one odorant by another, the greater the similarity of the stimulating properties of the two odorants (Cheesman et al, 1956; Le Magnen, 1948; Moncreiff, 1956; Pfaffmann, 1951). The manner and degree to which the odorants cause the receptors to adapt may not result from a simple mechanism because even if two different odorants are matched in subjective intensity, their cross-adapting effects may be asymmetric. For example, pentanol seems to have a strong cross-adapting effect on propanol, whereas propanol has only a small cross-adapting effect on pentanol (Cain and Engen, 1969).

Odor mixtures

Perfumes and chefs are involved in the mixing of odorants, and much of what is known in this area is in the realm of art rather than science. When two or more odorants are mixed, several sensory events may be reported (Mozell, 1971). First, the odorants may be discerned as being distinct. Second, an entirely new odor may develop that resembles the components but does not smell exactly like either of them. Third, one odor may mask the other. A fourth possibility, neutralization, would result if no odor were perceived, but the existence of this last phenomenon is controversial. Laing (1987) investigated the effect of intensity and quality perception of odorants in binary mixtures. They found that the odorant with the highest intensity always predominated or was the only component perceived. Both odorants were perceived, however, when the intensities of both components were approximately equal.

Clinical Olfactory Problems

Anosmia, parosmia, and phantosmia

Life for the person with anosmia has very "flat" quality to it. Patients say that they select food by texture, color, and custom. Some state, for example, that they must identify sour milk by its lumpy character. Others do not use perfumes for fear of overapplication. Many express concern regarding fire and noxious or dangerous gases, and in fact most anosmic patients have been involved in at least one accident stemming from this problem. Smoke alarms are an absolute

necessity for these people.

In contrast to this lack of sensory input, the individual with parosmia must live with distorted odors and the person with phantosmia perceives often foul-smelling odors all the time, even when eating. These people are miserable and will spend a great deal of time and money trying to rid themselves of their problem, often without success. As might be expected, some of these people whose sense of smell is dysfunctional will have dietary problems such as malnutrition, obesity, and anorexia (Mattes et al, 1990; Schiffman, 1983b).

Human olfactory dysfunctions

The report of the Panel of the Communicative Disorders to the National Advisory Neurological and Communicative Disorders and Stroke Council estimates that approximately 2 million American adults have disorders of taste and smell. The literature lists more than 200 conditions that have been associated with changes in chemosensory ability (Doty, 1979; Feldman et al, 1986; Schiffman, 1983a, 1983b; Scott, 1989b). To better understand these clinical chemosensory problems, multiple chemosensory centers have been established over the past decade. They have had the dual role of evaluating and treating patients and integrating basic science research into the effort. Using careful histories, physical examinations, chemosensory testing, and imaging studies, these centers have categorized the majority of patients with olfactory losses into etiologic categories (Table 36-1).

Although these centers differ as to the percentage of patients placed within each etiologic category, these differences are thought to reflect the particular type of patient seen at the center and not a difference in disease pattern across the country (eg, Heywood et al are associated with a major head trauma center). The following sections will describe the etiologic categories in detail. Those rare patients who have a distortion of their sense of smell (parosmia or phantosmia) with no change in intensity are not included in the above classification.

Obstructive nasal and sinus disease

Total nasal obstruction, such as caused by nasal polyps (Fig. 36-11), extreme mucosal swelling (Fig. 36-12), or simply finger occlusion of the nostrils will produce anosmia. When the obstruction is released, olfactory ability should return (Fig. 36-13), although the minimal nasal opening at which this occurs is not known. The location of this opening, or the area through which air flows to get to the olfactory cleft, is thought to be medial and anterior to the lower part of the middle turbinate (Leopold, 1988; Leopold et al, 1987). This area may function as a regulator of airflow to the olfactory cleft, and changes in its anatomy clearly affect olfactory ability. Consequently, obstruction at this area or above it by swollen mucosa, polyps, tumors, or nasal bony deformities can decrease or eliminate olfactory ability (Beninger, in press; Proetz, 1953; Scott, 1989b). This sometimes occurs even when the lower nasal cavity appears normal. It has been known that systemic steroid treatment will reverse anosmia in most patients with nasal obstruction that is caused by nasal polyps and chronic rhinitis (Davidson et al, 1987; Goodspeed et al, 1983; Hotchkiss, 1956; Scott, 1989b). Although treatment with chronic systemic

steroids has many drawbacks (Scott, 1989b), a 1- or 2-week course may serve as a diagnostic test for nasal disease. What is still unclear is the etiology of anosmia in the rare patient with a patent nasal airway whose olfactory ability can be improved by chronic systemic steroids (Jafek et al, 1987).

Table 36-1. Spectrum of olfactory loss at four chemosensory centers

1. Goodspeed et al (1987) (441 patients)
2. Davidson et al (1987) (63 patients)
3. Leopold et al (198 patients)
4. Heywood et al (1990) (133 patients)

Etiologic category	1.	2.	3.	4. in %
Obstructive nasal and sinus disease	30	33	29	20
Post-URI	19	32	15	17
Head trauma	9	10	19	32
Aging	0	0	8	6
Congenital	0	5	8	0
Toxins	1	11	3	0
Miscellaneous	14	10	8	16
Idiopathic	26	0	10	10

Although several authors have proposed that traumatic nasal cavity deformity can cause olfactory loss (Bramley, 1972; Martinkenas, 1976; Skopina et al, 1979), none of these reports employed reproducible olfactory testing, nor was any meaningful change in olfactory ability brought about by surgical changes in the nasal anatomy, so the olfactory losses reported may have been caused by neural problems. In my experience, it is rare to identify an individual whose nasal anatomy is so deformed from external trauma that not even a small amount of air can reach olfactory cleft. Scarring from previous surgery between the middle turbinate and the nasal septum, however, can be very effective in closing off the olfactory area to airflow.

Olfactory loss following upper respiratory infection

Many people will volunteer that at one time or another they have lost their sense of smell completely during an upper respiratory infection (URI). In general, these olfactory losses are due to nasal airway obstruction and will resolve when the nasal airway becomes patent again (1 to 3 days). Of greater concern is the small number of patients whose olfactory ability never recovers after the other symptoms of the URI resolve. These people tend to be otherwise healthy individuals, in the fourth, fifth, or sixth decade of life, and are overwhelmingly female (70% to 80%) (Davidson et al, 1987; Goodspeed et al, 1987; Hendriks, 1988; Leopold et al, unpublished data). The reason for this female preponderance is unclear but may related to the fact that women tend to have more URIs (Leopold et al, 1991a). Biopsies of the olfactory cleft in these patients show either decreased numbers of olfactory receptors or a complete absence of them (Jafek et

al, 1990b; Yamagishi et al, 1988). The prognosis for recovery from this olfactory loss is generally poor. Hendriks (1988) combined several reported studies of olfactory patients and found that approximately one third of the patients recovered their olfactory ability, regardless of whether they were treated or not. The problem with these studies is that an upper nasal obstruction from mucus or swollen mucosa may remain after the URI has resolved. Without concurrent imaging of the nasal cavity, it would be impossible to determine if a return of olfactory ability after a URI loss was due to clearing of the olfactory cleft or recovery of neural function.

Head trauma

Review of several large series of mostly adult head trauma patients (containing both minor and major trauma) reveals that the reported incidence of olfactory loss is between 5% and 10% (Leigh, 1943 (1000 cases); Hughes, 1964 (1800 cases); Sumner, 1964 (1167 cases); Zusho, 1982 (5000 cases)). In contrast to this, the rate of olfactory loss after childhood head trauma has been reported to be 3.2% (transient) and 1.2% (permanent) (Jacobi et al, 1986 (741 cases)). The degree of olfactory loss is generally associated with the severity of the trauma; however, even minor trauma can produce total anosmia (Caruso et al, 1969; Hasegawa et al, 1986). Most studies of patients who complain of olfactory loss after trauma find the average loss to be in the anosmic range (Davidson et al, 1987; Leopold et al, unpublished data). Fikentscher and Müller (1985), who classified 77 of 122 patients as anosmic, also support this tendency for the posttraumatic loss to be complete. The degree of olfactory loss is also partly determined by the site of cranial trauma. Frontal blows most frequently cause olfactory loss; however, total anosmia is five times more likely with an occipital blow (Hendriks, 1988; Sumner, 1964). The onset of a traumatic olfactory loss is generally immediate, although in some instances the patient either does not appreciate the loss or does not experience the loss until months after the injury (Leopold et al, unpublished data; Schechter and Henkin, 1974). Recovery of olfactory function is less than 10% according to most large studies, and it can be variable.

The exact injury to the olfactory system produced by trauma is unknown, although shearing of the olfactory nerves as they exit the top of the cribriform plate is a popular theory (Hagin, 1967). New information from biopsies of olfactory epithelium in humans who sustained a traumatically induced olfactory loss has recently become available (Jafek et al, 1989; Yamagishi et al, 1988). After trauma the olfactory cells are generally distorted, have proliferation of axons and axon tangles in the lamina propria, and have few olfactory knobs and cilia. These findings suggest the following scenario: (1) the olfactory nerves were damaged at the time of the trauma, perhaps at the cribriform plate; (2) the normal response of the olfactory nerves is to regenerate, but the axons cannot (for some unknown reason), reach the olfactory bulb; and (3) without this connection with the bulb, the cells will not produce olfactory knobs or cilia. The key, therefore, in helping these people is to reestablish contact between the olfactory axons and the olfactory bulb. Presently, however, there is no known method to accomplish this task. Another possible area of olfactory system injury after head trauma may be in the frontal cortex. In a study of 40 patients who had traumatic total anosmia, all had major vocational problems (Varney, 1988). Most of these patients demonstrated psychosocial defects associated with frontal cortex injury. Similarly, Levin et al (1985) observed impaired olfactory recognition in patients who had a

traumatic hematoma or contusion in the frontotemporal region.

Aging

Although older individuals can have an olfactory loss from any of the other causes discussed here, they also can have losses caused by dementia-related diseases and from the aging process itself. Olfactory identification ability has been shown to drop off sharply in the sixth and seventh decades of life such that more than half of those 65 to 80 years old show major olfactory declines (Stevens and Cain, 1987). This pattern of change with respect to age is similar to that seen for visual acuity and speech intelligibility (Doty et al, 1984c). Olfactory thresholds have also been found to decline with age, this effect being slightly less dramatic in females than in males (Cain and Murphy, 1987; Deems and Doty, 1987; Stevens and Cain, 1987; VanToller and Dodd, 1987). From the National Geographic Smell Survey, Wysocki and Gilbert (1989) have determined that the degree and rate of olfactory loss is odorant specific and varies from individual to individual. Other measured effects of aging on the sense of smell include decreased magnitude matching (Stevens and Cain, 1987), changes in the perception of pleasantness (Wysocki and Gilbert, 1989), and the ability to discriminate flavor in everyday foods (Cain et al, 1990; Schiffman, 1979).

The perceptual losses in olfactory ability that accompany aging are not surprising when the anatomic changes are noted. Bhatnagar et al (1987) carefully studied olfactory bulbs from individuals aged 25 to 95. From a total of 50.935 mitral cells at age 25, they counted a linear decline that averaged 520 cells per year. Likewise, from a total olfactory bulb volume of 50.02 mm³ at age 25, they noticed a decline of 0.19 mm³ per year. In addition to the decline in the number of cellular elements, Liss and Gomez (1958) also noted extensive degeneration in the bulb with aging.

There are at least two dementia-related diseases that are often accompanied by a smell disorder. Alzheimer's disease and Parkinson's disease. In patients with these diseases, it is likely that there has been some damage to the olfactory bulb or the central olfactory cortex and that this damage is, at least in part, responsible for the accompanying loss in olfactory detection and recognition ability (Doty et al, 1987). Alzheimer's disease is characterized by the presence of neurofibrillary tangles and neuritic plaques in most of the central olfactory pathways (Esiri et al, 1986; Kishikawa et al, 1990; Mann et al, 1988); these tangles and plaques are presumed to account for the clinical deficits of the disease (Harrison and Pearson, 1989; Pearson et al, 1985). Furthermore, as Pearson et al (1985) have pointed out, the involvement by the olfactory system is in striking contrast to the minimal abnormality seen in other areas of the brain. This has raised the possibility that the olfactory system is the portal of entry for an environmental agent that causes the disease (Ferreya-Moyano and Barragan, 1989). Recently identified abnormalities in the nasal olfactory epithelium may give additional support for this theory (Talamo et al, 1989). An alternative theory is that the olfactory system is simply attacked preferentially over other neural elements (Doty, 1989). Recently there have been a number of nonmotor defects identified in patients with Parkinson's disease. A reduction in the ability to detect and identify odorants is one of these defects. The olfactory changes have been shown to be independent of the cognitive

and motor symptoms (Doty et al, 1989), and they occur early in the disease. Because the loss of olfactory ability also occurs early in Alzheimer's disease, clinical testing of olfactory ability may be an important early signal for the development of these diseases.

Congenital

The usual history of the person with a total congenital loss of the sense of smell is that he or she is otherwise healthy and began to learn at about age 8 that friends, parents, and siblings could perceive something he or she could not. Most of these individuals have their other chemosensory functions intact, so that pungency, irritating odors, and tastes can be detected normally (Jafek et al, 1990). Many more people have an isolated loss of sensitivity to a particular chemical or group of chemicals (also known as a specific anosmia), for example, musks, trimethylamine (a fishlike odor), hydrogen cyanide (almondlike), n-butyl mercaptan (an additive to natural gas), and isovaleric acid (a locker-room odor) (Amoore, 1969; Patterson and Lauder, 1948).

Jafek et al (1990a) have proposed that the pathophysiology of congenital olfactory loss is due to a degeneration or atrophy of the olfactory epithelium and/or the olfactory bulb late in the development process. They base this theory on the total lack of peripheral receptors or supporting cells and the routine finding of respiratory epithelium in olfactory cleft biopsies from people with a history consistent with a congenital loss. On olfactory testing, individuals in this congenital group scored either at or slightly better than chance performance (Davidson et al, 1987; Jafek et al, 1990a; Leopold et al, 1991b). Because individuals from other etiologic groups (eg, head trauma, post-URI) have been shown to have at least some olfactory epithelium (albeit often abnormal), it is not surprising that this congenital group has the lowest olfactory scores of all the etiologic groups.

Familial anosmia associated with premature baldness and vascular headaches has been reported by Singh et al (1970) as a dominant inheritance with varying penetrance. Complete anosmia without other abnormalities has been reported as being autosomal-dominant by Lygonis (1969), although the lack of continued transmittal of complete anosmia through families again suggests varying penetrance. Perhaps the best known type of congenital anosmia is associated with hypogonadotrophic hypogonadism known as *Kallmann's syndrome* (Kallmann et al, 1944; Kanai, 1940). At least some of these patients have been shown to have agenesis of the olfactory bulbs and stalks and incomplete development of the hypothalamus (de Morsier, 1962; Dewes et al, 1987). The one Kallmann's patient studied by Jafek et al (1990a) also had no olfactory epithelium in the olfactory cleft. Other defects sometimes seen in Kallmann's syndrome include renal abnormalities, cryptorchidism, deafness, midline facial deformities, and diabetes. The existence of this syndrome brings to light the strong association between sexual development and olfaction in other mammals. Male mice, for example, will not show mating behavior or sexual development if their olfactory bulbs have been removed shortly after birth (Rowe and Edwards, 1972; Rowe and Smith, 1972; Whitten, 1956).

Toxic exposure

The history of olfactory loss in conjunction with exposure to a particular chemical is presently the clinical method used to make the diagnosis. The loss may occur over a period of days, as was the case for a dentist who was using a new compound for dental work. Conversely, it may be years until the loss is apparent, such as with exposure to formalin. Even common substances, such as cigarette smoke, can be associated with olfactory loss (Frye et al, 1990). The literature has many reports of olfactory loss after exposure to toxins, some of which are reversible, and some permanent (Ahlstrom et al, 1986; Davidson et al, 1987; Sandmark et al, 1989; Schwartz et al, 1989). Scott (1989b) and Feldman et al (1986) have listed many of the known agents related to olfactory loss, and their list is long. The majority of the agents are either gases or aerosols and enter the nose with the respiratory air stream. Obviously, the concentration and length of time of the exposure need to be considered, and employers need to be aware of these factors (Fikentscher and Seeber, 1989).

Neoplasms

Both intranasal and intracranial tumors can affect the sense of smell. The intranasal tumors most commonly seen are inverting papillomas, adenomas, squamous cell carcinomas, and esthesioneuroblastomas (Skolnik et al, 1966). These tumors decrease olfactory ability mostly by blocking the airflow to the olfactory cleft. Intracranial meningiomas, pituitary tumors, and gliomas can cause local destruction to the olfactory apparatus. Approximately 25% of temporal lobe tumors have been estimated to cause an olfactory disturbance (Furstenberg et al, 1943). Symptoms of nasal obstruction, epistaxis, anosmia, hyposmia, visual lesions, or other central nervous system signs should be a warning of these tumors. Uninasal olfactory testing is a good way to diagnose them.

Psychiatric disorders

The presence of olfactory complaints in psychiatric patients is being reported more often than in the past (Kerekovic, 1972). Patients with depression, schizophrenia, and hallucinations may have olfactory complaints as part of their psychiatric disorder. Although depressed patients do have some altered gustatory ability, their ability to identify odorants is generally normal (Amsterdam et al, 1987). Thus, the source of the olfactory complaints these people have is likely to be located in the central nervous system, and it may be that the same chemicals that are thought to cause the symptoms of depression affect the neural connections between the limbic system and the hypothalamus (Jesberger and Richardson, 1988). Pryse-Phillips (1971) differentiates "intrinsic" olfactory hallucinations (in which the patient believes the smells emanate from his or her own body) from "extrinsic" hallucinations (in which the odors seem to come from a source other than the patient's own body). The olfactory reference syndrome describes patients who are obsessively concerned about minor or absent odors. Because these concerns are often in reference to body odor, these people bathe frequently and use perfumes in an abnormal way. In the Marcel Proust syndrome, individuals conjure up memories based on odors in such dramatic ways as to interfere with their daily routines. Careful attention to the patients' descriptions of

their concerns will often point out a need for psychiatric referral.

Parosmia and phantosmia

Distortion of the sense of smell clearly bothers patients more than the loss of the sense of smell. It is difficult for patients with parosmia to learn new names for the smells of familiar items. They are disturbed that "nothing smells normal". On the other hand, patients with phantosmia might continuously perceive an unpleasant odor, such as rotten eggs or feces. Both these distortions can be intermittent or continuous and can be brought on by specific triggers, such as strong odors, loud sounds, or stress. Several patients have been able to halt the onset of a phantosmia by tickling the inside of their noses, such as with a paper clip. Parosmias and phantosmias have been reported to accompany many disorders, and some of these are associated with brain or psychiatric disease, such as temporal lobe tumors or seizures (Scott, 1989a; Zilstorff and Herbild, 1979). For this reason, they have been thought of as being central nervous system origin. Recent studies by Leopold et al (1991b) suggest that some individuals with phantosmia may have diseased neurons in the peripheral olfactory system and are amenable to treatment. The etiology of phantosmias and parosmias is most often associated with a specific URL, head trauma, or the aging process (Fikentscher and Rasinski, 1986; Leopold et al, 1991b). Other investigators have also noted it in patients with nasal disease (Scott, 1989b; Seiden et al, 1988). Patients with these distortions of odor quality are more likely to be female and generally will have decreased olfactory ability when tested (Leopold et al, 1991b; Scott, 1989b).

Medications

Although medications seem to affect the taste system more than the olfactory system, there are many that can cause olfactory dysfunction (Table 36-2). Usually the olfactory ability will return after the offending medication is discontinued, but sometimes the change is permanent.

Surgery

Alterations of either the respiratory airflow path or the region around the olfactory nerves can be expected to affect olfactory ability. Although septal deformities that can affect olfactory ability have been described (Shevrygin and Maniuk, 1974), and septal surgery has been reported to improve olfactory ability (Kittel and Waller, 1973; Shevrygin, 1973), deformities severe enough to obstruct a nasal airway are relatively rare. Losses of olfactory ability after rhinoplasty have also been reported. Champion (1966) reviewed the records of 100 consecutive rhinoplasty patients and found that 20% of them complained of the loss of the sense of smell from 6 to 18 months after surgery; 95% of these were temporary. No olfactory testing was used in his study. Goldwyn and Shore (1968) tested 97 patients before and after nasal surgery and found 3 patients with decreased postoperative olfactory ability. These losses could be caused by neural damage at the time of the surgery or the narrowing of the nasal airways by anatomic changes or scar tissue (Rous and Kober, 1970).

Table 36-2. Drugs affecting taste and smell

Classification	Drug
Amebicides and anthelmintics	Metronidazole; niridazole
Anesthetics, local	Benzocaine, procaine hydrochloride (Novocain), and others; cocaine hydrochloride; tetracaine hydrochloride
Anticholesteremics	Clofibrate
Anticoagulants	Phenindione
Antihistamines	Chlorpheniramine maleate
Antimicrobial agents	Amphotericin B; ampicillin; cefamandole; Griseofulvin; ethambutol hydrochloride; lincomycin; sulfasalazine; streptomycin; tetracyclines; tyrothricin
Antiproliferative, including immunosuppressive agents	Doxorubicin and methotrexate; azathioprine; carnustine; vincristine sulfate
Antirheumatic, analgesic-antipyretic, antiinflammatory agents	Allopurinol; colchicine; gold; levamisole; D-penicillamine; phenylbutazone; 5-thiopyridoxine
Antiseptics	Hexetidine
Antithyroid agents	Carbimazole; methimazole; methylthiouracil; propylthiouracil; thiouracil
Agents for dental hygiene	Sodium lauryl sulfate (toothpaste)
Diuretics and antihypertensive agents	Captopril; diazoxide; ethacrynic acid
Hypoglycemic drugs	Glipizide; phenformin and derivatives
Muscle relaxants and drugs for treatment of Parkinson's disease	Baclofen; chlormezanone; levodopa
Opiates	Codeine; hydromorphone hydrochloride; morphine
Psychopharmacologic, including antiepileptic, drugs	Carbamazepine; lithium carbonate; phenytoin; psilocybin; trifluoperazine
Sympathomimetic drugs	Amphetamines; phenmetrazine theoclate and fenbutrazate hydrochloride (combined)
Vasodilators	Oxyfedrine; bamifylline; hydrochloride
Others	Germine monoacetate; idoxuridine; iron sorbitex; vitamin D; industrial chemicals, including insecticides.

Patients who undergo a total laryngectomy have inspired air rerouted away from the nasal cavity. These patients complain of decreased olfactory ability (Reed, 1961), but some can perceive odors when the stimulus is under their noses (Gilchrist, 1973). Mozell, Schwartz, and

their colleagues (1983, 1986, 1987) have shown that olfactory ability can be restored to patients after laryngectomy by shunting respired air again through their noses, which indicates that the olfactory receptors were intact and functional even after many years.

Much of the neurosurgery in the region of the olfactory bulbs has been associated with a total and permanent loss of olfactory ability. However, new techniques are being developed for preservation of the olfactory tract (Sailer and Landolt, 1987; Tigliev et al, 1986).

Idiopathic

After an extensive workup including many tests, some patients still have no obvious reason for their olfactory dysfunction. They are usually young or middle-aged adults in otherwise good health. Some olfactory biopsies from patients in this category have shown the presence of olfactory epithelium, but the changes observed are not characteristic enough to be diagnostic (Yamagishi et al, 1988, 1990).

Diagnostic assessment

The most important thing the physician can offer the patient with an olfactory dysfunction is an accurate diagnosis and concern for his or her plight. In obtaining the medical history, it is important to have the patient estimate the degree of olfactory loss and the time over which the loss occurred (eg, days, weeks, or months). Events that occurred around the time of the loss, such as trauma or URI, also need to be determined. A thorough review of systems and general medical health will help to rule out side effects of medications and problems caused by diseases such as hypothyroidism. By carefully assessing the patient's problem, a seemingly unrelated entity such as a metabolic disease can be diagnosed in a patient previously thought to have psychologic problems (Leopold et al, 1990). The physical examination should include special attention to the nose, mouth, and the neurologic system. Nasal endoscopy has been particularly useful in assessing the nasal airways in the region just below the olfactory cleft. Mandatory tests for the workup of patients with chemosensory complaints include testing of their gustatory and olfactory ability (Cain et al, 1988; Smith, 1988). In general, identification tests (like the SIT test, Sonsonics, Inc, Haddenfield, NJ) have been more useful than threshold tests in the clinical situation (Cain et al, 1988). Bilateral and uninasal olfactory testing has been useful in detecting both nasal and cranial tumors and unsuspected neural losses (Furukawa et al, 1988b). If the patient's medical situation warrants blood testing (such as for thyroid hormone levels), it should be performed, but routine tests have not been useful (Goodspeed et al, 1987). Rhinomanometry can be useful in assessing the general status of the nose; however, if the upper nasal airways are patent, any small nasal airflow will allow olfaction to occur. If an anatomic deformity or obstruction is suspected, if there is any history of nasal or sinus disease, or if the diagnosis is not perfectly clear, a computerized tomography (CT) scan of the nasal and sinus cavities should be performed in the coronal plane. Magnetic resonance (MR) scans of this region are not able to permit visualization of the fine bony detail of the upper nasal cavity, but they can be useful for soft tissues, sometimes including the olfactory sulci (Klingmuller et al, 1987; Suzuki et al, 1989). Plain radiographs of this region are too imprecise to be of any help in the workup. Another

advantage of the coronal CT scan is that it helps to rule out tumors or deformities in the anterior cranial fossa. In a few centers around the country, olfactory biopsies are being performed to assess the status of the olfactory epithelium. These biopsy studies require a great deal of time and expertise and are still considered research studies (Jafek et al, 1989; 1990b; Yamagishi et al, 1988; 1990).

Management

The major olfactory dysfunction for which treatment has been useful is that caused by nasal disease. As previously described, the problem is obstruction of airflow to the olfactory cleft. Treatment aimed at opening the air passageways while preserving the olfactory epithelium will improve olfactory ability. Medical therapy, including intranasal steroids, antibiotics, and allergic therapy, is the mainstay of management. Oral steroids have been particularly useful in shrinking thickened nasal mucosa; however, the side effects of this treatment need to be weighed against its potential benefits (Scott, 1989b). Patients who are resistant to medical therapy or those who have tumors often can benefit from surgical therapy. Tumors are treated according to usual oncologic principles. Often the nasal disease is associated with (or perhaps caused by) adjacent ethmoid sinus disease. Functional ethmoidectomy, often conducted with the use of an endoscope, can improve the health of these sinuses, and in turn, allow the olfactory cleft to open (Jafek and Hill, 1989; Yamagishi et al, 1989a). Even those patients who have had surgery may need long-term medical treatment to control the disease and prevent recurrence.

For patients who have been placed in any of the other diagnostic categories, there is no proven therapy. In general, the problem with these patients is either a total lack of olfactory receptors (eg, congenital) or olfactory receptors that do not seem to be functioning normally (eg, trauma). Multiple treatments have been proposed, often using vitamins or minerals. Vitamin A was thought to be an effective treatment because (1) it is necessary for the repair of epithelium, (2) white rats apparently become anosmic on a diet deficient in vitamin A (Le Magnen and Rapaport, 1951), and (3) assays done on mammalian olfactory epithelium showed considerable amounts of vitamin A (Duncan and Briggs, 1962). In an uncontrolled study, Duncan and Briggs (1962) used vitamin A successfully to restore at least partial olfactory ability in 50 out of 56 of their subjects. Unfortunately, other observers have been unable to reproduce their success (Hendriks, 1988; Leopold et al, unpublished data). B vitamins have also been tried for the treatment of anosmia, once again without success (Duncan and Briggs, 1962; Mendelsohn, 1967).

Mackay-Sim and Dreosti (1989) have shown that zinc-deficient adult mice failed to show a food odor preference. This supports the administration of oral zinc by Henkin et al (1981) as a treatment for losses of taste and smell associated with a zinc deficiency. It is known that severe zinc deficiency is rare and difficult to substantiate (Kay, 1981). Nevertheless, occasional reports of patients who have improved on zinc therapy are available (Cassirer, 1981; Krueger and Krueger, 1980). These reports must be evaluated, however, with the understanding that some olfactory disorders do improve spontaneously. Indeed, in a randomized, double-blind crossover study of the effects of zinc on 106 patients with taste and smell problems, Henkin et al (1976) noted that zinc was no more effective than placebo. At the present time, few chemosensory

centers are suggesting that zinc is useful for olfactory disorders (Scott, 1989b). Henkin (1976) has also suggested that aminophylline is useful for anosmic and hyposmic patients. This suggestion is based on the observation that cyclic AMP plays a role in the transduction of olfactory responses. Unfortunately, corroborative data supporting its use are not available.

Once patients have been placed in one of the nontreatable groups, they should be reassured that there are others with similar deficits. Because olfaction plays such an important role in the appreciation of foods, these patients should be counseled on possible ways to improve the variety of seasoning of their diet to enhance whatever sensory modalities remain (eg, emphasizing the taste, color, texture, viscosity, and "mouth feel" of foods). Attempts should be made to ensure that the normosmic person(s) living with them understand(s) the problem and can be relied upon to volunteer information of social concern regarding odors. Smoke and fire detectors are mandatory. Anosmic persons living alone should elicit the confidential help of friends on matters of odor. The dangers of natural gas and liquid petroleum gas can be avoided by switching to electric appliances and nonexplosive heating or cooling fuel (Cain and Turk, 1985).

The treatment of phantosmia is varied. In Europe, Zilstorff (1966) and Fikentscher and Rasinski (1986) have used topical cocaine hydrochloride directly on the olfactory mucosa; however, multiple retreatments have been required, and other clinicians have been unable to duplicate their results (Scott, 1989b). In addition, I have documented the total loss of olfactory ability in one patient who used this treatment daily over several years. Kaufman et al (1988) have done olfactory bulbectomies via a neurosurgical craniotomy approach to alleviate the phantom odor. While the patients who have had this surgery are pleased to be rid of their phantom odor, they are left with no olfactory ability on the operated side. If both sides are operated upon, they will be totally anosmic. Leopold et al (1991b) have successfully treated phantosmia by removing olfactory epithelium from the underside of the cribriform plate. The advantage to this procedure seems to be that the olfactory ability is not irreversibly destroyed.

Summary

Although the basic mechanisms of olfaction are still being discovered, what has already been learned forms an exciting foundation for further research. The process of odorant delivery to the receptors differs from one person to another and may be an adaptation to the differences in upper nasal cavity anatomy. Although the receptors regenerate throughout one's adult life, why does this process not continue after head trauma? How does the olfactory system distinguish the thousands of odorants to which humans are exposed? What is the relationship of the olfactory loss in Parkinson's disease to the progression of the disease? The answers to these questions and many others are being explored. By evaluating and diagnosing patients with olfactory problems, a better understanding of the olfactory system is being obtained, and these patients are being helped in the process.