Paparella: Volume III: Head and Neck

Section 2: Disorders of the Head and Neck

Part 1: Nose and Paranasal Sinuses

Chapter 9: Taste and Smell Dysfunction

David V. Smith

The patient presenting with a complaint of taste or smell dysfunction is often difficult to diagnose and treat. Sometimes this type of patient has been to a number of health professionals in an unsuccessful attempt to get help for the problem. Much of the difficulty in dealing with such a patient lies in a general lack of knowledge about taste and smell and their disorders. A dysfunction of taste or smell can occur as a secondary process in a number of disease states. At other times, a patient's primary complaint is a reduced ability to taste or smell or a distorted chemosensory experience. Several recent reviews have addressed these clinical problems (Doty, 1979; Doty and Kimmelman, 1986; Doty and Snow, 1987; Feldman et al, 1986; Kimmelman, 1986; Leopold, 1986a; Meiselman and Rivlin, 1986; Schiffman, 1983a, 1983b), and others have dealt with the clinical measurement of taste and smell dysfunction (Bartoshuk et al, 1983; Cain et al, 1983; Meiselman and Rivlin, 1986). This chapter presents information on the basic physiology and anatomy of taste and smell, on the measurement of chemosensory function in a clinical setting, and on some of the known common causes of taste and smell dysfunction.

Basic Anatomy and Physiology of Taste and Smell

Basic Anatomy of the Gustatory System

The sense of taste is mediated through chemical stimulation of taste buds, which are composed of receptor cells, supporting cells, and nerve fiber terminals. Taste buds are often contained within distinct papillae, particularly those on the tongue. At the ultrastructural level, at least two kinds of cells can be discerned within the taste bud. They are termed *dark cells* and *light cells* on the basis of the presence or lack of dense granules in their apical portion (Murray, 1971). These receptor cells are modified epithelial cells that arise continually from an underlying layer of basal cells. It is not clear, primarily because the cells are in a constant state of turnover, whether the cell types identifiable on structural grounds are different cell types or a single type at different maturational stages. The cells in the taste bud are arranged in a concentric columnar fashion with their apical microvilli projecting toward a pore that opens through the epithelium into the oral cavity. The base of the taste bud is penetrated by branches of the afferent nerve, which make synaptic contact with the receptor cells (Murray, 1971; Williams and Warwick, 1975). Taste receptor cells undergo constant turnover, with replacement cells arising through mitosis of the underlying basal cells. In the rat, the life span of a taste cell in a fungiform papilla is approximately 10 days (Beidler and Smallman, 1965). A single nerve fiber may innervate more than one taste papilla, each of which may contain many taste buds, each innervated by several afferent fibers (Beidler, 1969). The afferent nerve maintains a trophic influence over the taste buds, which will degenerate if their nerve supply is removed (Guth, 1971). Although the innervation by gustatory nerve fibers is necessary to

maintain the integrity of the taste bud, the specificity of the receptor cells is not determined by the particular nerve involved but by the epithelium itself (Oakley, 1967).

Taste buds are found on the tongue in fungiform papillae anterior to the sulcus terminalis and in circumvallate and foliate papillae posterior to this boundary (Arvidson, 1979; Bradley, 1971; Miller, 1977; Miller and Smith, 1984). There are also taste buds on the soft palate, pharynx, epiglottis, and upper third of the esophagus (Bradley, 1971; Miller and Smith, 1984; Nilsson, 1979). In humans, there are an average of 33 fungiform papillae on the anterior portion of the tongue, containing approximately 114 taste buds, although there is considerable variation among individuals (Miller, 1986). The 8 to 12 circumvallate papillae contain about 250 taste buds each, for a total of nearly 3000 taste buds, and the foliate papillae have about 1280 taste buds (Bradley, 1971; Mochizuki, 1939). Although taste buds have been described on the soft palate of human adults only in biopsy material and only in very small numbers (Nilsson, 1979), human infants are reported to have about 2583 taste buds in the pharynx and larynx and on the soft palate (Lalonde and Eglitis, 1961). These numbers, however, are derived from very few studies. On the tongue of adult rhesus monkeys (fungiform, circumvallate, and foliate papillae), there are approximately 8.000 to 10.000 taste buds, which are maintained well into old age (Bradley et al, 1985). A complete quantification of the taste bud distribution in the hamster, an animal commonly used for electrophysiologic investigation of taste, demonstrated a total of 723 taste buds, with 18 per cent located in fungiform papillae, 23 per cent in a single valate papilla, 32 per cent in the foliate papillae, 12 per cent on the soft palate, and 10 per cent on and near the epiglottis (Miller and Smith, 1984). An additional 5 per cent are located in small numbers on the buccal walls and the sublingual organ and in the nasoincisor ducts. Most electrophysiologic studies of taste have employed stimulation of the fungiform papillae, even though the majority of taste buds in all mammalian species studied are located in other areas.

Taste receptors are innervated by branches of three cranial nerves. Taste buds in the fungiform papillae on the anterior portion of the tongue are innervated by the chorda tympani branch of the facial nerve, and those on the soft palate are innervated by its greater superficial petrosal branch. The cell bodies of these afferent fibers are located in the geniculate ganglion and project centrally into the rostral pole of the nucleus tractus solitarius (Contreras et al, 1982; Hamilton and Norgren, 1984; Williams and Warwick, 1975). Circumvallate and most foliate taste buds are supplied by the glossopharyngeal nerve, although the most rostral foliate taste buds are innervated by the chorda tympani nerve. Afferent fibers of the glossopharyngeal nerve project through the inferior glossopharyngeal (petrosal) ganglion to the nucleus of the solitary tract just caudal to, but overlapping with, the facial nerve termination (Contreras et al, 1982; Hamilton and Norgren, 1984). Taste buds on the epiglottis, caudal pharynx, and esophagus are innervated by the internal portion of the superior laryngeal branch of the vagus nerve. Afferent fibers from the superior laryngeal nerve project via their cell bodies in the inferior vagal (nodose) ganglion to the nucleus tractus solitarius caudal to, but overlapping with, the glossopharyngeal nerve termination (Contreras et al, 1982; Hamilton and Norgren, 1984; Hanamori and Smith, 1986).

From this termination within the nucleus of the solitary tract, secondary gustatory fibers arise to project rostrally more or less parallel to the projection of general visceral sensation, arising from the more caudal aspects of the solitary nucleus (Norgren, 1985). In most mammalian species, there is a third-order projection into the parabrachial nuclei in the

pons, from which fibers arise to project via a classic sensory path to the posterior ventromedial nucleus of the thalamus and then to the insular cortex (Norgren, 1985). In addition to this thalamocortical projection, fibers also travel from the pons into areas of the ventral forebrain involved in feeding and autonomic regulation, including the lateral hypothalamus, central amygdala, and the bed nucleus of the stria terminalis (Norgren and Leonard, 1973). Recent work, however, has suggested that in the monkey, taste fibers bypass the pontine relay and project directly to the thalamus (Beckstead et al, 1980). There are, unfortunately, no modern data on the anatomy of these projections in humans.

Basic Anatomy of the Olfactory System

The sense of smell is mediated through the stimulation of olfactory receptor cells by volatile chemicals. The olfactory receptors are contained in a neuroepithelium, which is located at the top of the nasal vault, along the upper portion of the nasal septum and over the superior turbinate and the lateral walls above it (Williams and Warwick, 1975). Afferent information from these receptors is carried to the olfactory bulbs by cranial nerve I. In order to stimulate the olfactory receptors, airborne molecules must pass through the nasal cavity, in which they are subjected to relatively turbulent air currents (Leopold, 1986a, 1986b). The duration, volume, and velocity of a sniff are all important determinants of an odor's stimulating effectiveness. Although these parameters differ markedly among individuals, they are quite constant for any one person (Laing, 1982). Once airborne volatiles have reached the olfactory region, they must then pass through the layer of mucus that covers the olfactory epithelium. The stimulating effectiveness of an odor is also determined to some extent by the relative partitioning of the odor between air and mucus (Laffort et al, 1974; Leopold, 1986a).

The olfactory receptors lie in a pseudostratified columnar epithelium, which is much thicker than the surrounding respiratory epithelium of the nasal cavity. This epithelium rests on a vascular lamina propria. Within the epithelium are bipolar olfactory neurons, microvillar cells, supporting cells, basal cells, and Bowman's glands (Graziadei, 1971; Jafek, 1983). Unlike taste receptor cells, which are modified epithelial cells, the olfactory receptors are primary sensory neurons. Their cell bodies lie in the basal two thirds of the epithelium, with their apical dendrites extending to the surface. At the peripheral ending, the receptor neuron swells slightly to form the olfactory knob, from which several olfactory cilia extend into the mucous layer (Jafek, 1983). Human olfactory cilia do not possess dynein arms, suggesting that they are immotile (Jafek, 1983). In other vertebrates, however, ciliary length and motility have been related to receptor age and development (Adamek et al, 1984; Gesteland et al, 1982). Immature cells, with relatively short cilia, display random and rapid ciliary motion. More mature neurons, with connection to the olfactory bulb, have longer, more slowly moving cilia. The most mature olfactory neurons have immotile cilia. The role of the olfactory cilia in receptor function is not clear, although it is thought that they at least provide an increased surface for odorant-receptor interaction. Basal to the receptor cell body, a nonmyelinated axon arises, joins a small bundle of other axons, and penetrates the basal lamina, at which point the bundles become ensheathed by Schwann cells. These bundles (fila olfactoria) join others to make up the 15 to 20 fascicles of the olfactory nerve, which pass through the cribriform plate to synapse in the olfactory bulb (Graziadei, 1971; Williams and Warwick, 1975).

The supporting cells of the olfactory epithelium appear to separate and partially wrap the receptor cells. Their surface, in humans and some other vertebrates, is covered with microvilli, which project along with the olfactory cilia into the mucous layer (Graziadei, 1971; Jafek, 1983). The microvillar cells, about one-tenth the number of the receptor neurons in humans, have microvilli on their apical surface projecting into the mucous layer (Jafek, 1983). Their basal end taper into a cytoplasmic extension that appears to project into the lamina propria. It is not known whether this projection is an axon, although the ultrastructural appearance of the microvillar cells appears to be neuronal (Jafek, 1983). Underneath these cells are the basal cells, which sit on a basement membrane just above the lamina propria (Graziadei, 1971; Jafek, 1983). The basal cells are stem cells for the replacement of the olfactory neurons (Graziadei, 1973), which in the mouse have a life span of approximately 40 days (Monti-Graziadei and Graziadei, 1979). Within the lamia propria are the secretory Bowman's glands, which provide a serous component to the mucous layer covering the olfactory epithelium. It is unknown whether these secretions play a role in olfactory transduction (Jafek, 1983). Olfactory receptor cells and their axons contain olfactory marker protein (OMB), which is unique to the olfactory pathway (Margolis, 1972). This protein is found in a number of mammalian species, including humans (Nakashima et al, 1985), and its expression depends upon the integrity of the olfactory pathway (Harding et al, 1978).

Olfactory information is carried via the first cranial nerve to the glomerular layer of the olfactory bulb. Here the first-order olfactory fibers make synaptic contact with dendrites of mitral and tufted cells, which are the output neurons of the olfactory bulb (Shepard, 1983). Axons from these cells project into the olfactory cortex, which is divided into five regions, including the anterior olfactory nucleus, the pyriform cortex, the olfactory tubercle, the corticomedial amygdala, and the entorhinal cortex (Shepard et al, 1981). These areas, in turn, have widespread interconnections with many areas of the brain, including the mediodorsal thalamus, hippocampus, hypothalamus, and other areas of the limbic system.

In addition to input from the olfactory epithelium, many odors give rise to activity in the trigeminal system through the stimulation of free nerve endings (Moulton and Beidler, 1967). The burning or irritation arising from stimuli like ammonia or hot peppers interacts with olfactory and gustatory input in what is known as the common chemical sense. Fibers in each of the three branches of the fifth cranial nerve carry information about intranasal or intraoral chemical irritation. These sensations usually remain intact in patients complaining of taste or smell dysfunction and can be useful in the assessment of the malingering patient (Doty, 1979).

Physiology of Taste

Many textbooks of physiology show a diagram of the human tongue that suggests that saltiness and sweetness are appreciated on the tip, sour on the sides, and bitterness on the back of the tongue. Although there are slight differences in the absolute threshold for different taste qualities in different regions of the tongue and palate (Collings, 1974), all taste qualities (salty, sour, sweet, and bitter) can be perceived in all regions. Further, across the anterior portion of the tongue, there is no interaction between the size of the area stimulated and the magnitude of sensation for the different qualities (Smith, 1971); that is, receptors for the various qualities are not differentially distributed across the tongue. The suggestion by von Bekesy (1966) that individual papillae are selectively responsive to different taste qualities

has been refuted by a number of investigators (Bealer and Smith, 1975; Harper et al, 1966; Kuznicki and Cardello, 1986; McCutcheon and Saunders, 1972).

A lack of specificity of single-taste papillae coincides well with the fact that individual papillae contain several taste buds, each of which is composed of a number of receptor cells. Electrophysiologic recordings from individual mammalian receptor cells have further demonstrated that even single-receptor neurons are responsive to more than one quality of taste (Ozeki and Sato, 1972; Kimura and Beidler, 1961). The receptor mechanisms for stimuli with different taste qualities must therefore coexist within a single cell. The nature of these transduction mechanisms is currently an area of much interest (DeSimone and Price, 1976; Kinnamon and Roper, 1987; Price and DeSimone, 1977; Roper, 1983).

Most of what is known about the neurophysiology of the mammalian gustatory system has been derived from studies on the input from the anterior portion of the tongue. Like individual receptor cells, single fibers in the chorda tympani nerve typically respond to more than one taste quality (Frank, 1973; Pfaffmann, 1955). Individual second- and third-order gustatory neurons in the nucleus tractus solitarius and parabrachial nuclei are similarly broadly tuned across taste quality (Smith, 1985; Smith et al, 1983; Travers and Smith, 1979, 1984; Van Buskirk and Smith, 1981). Recent work on fibers in the glossopharyngeal nerve also demonstrates a lack of stimulus specificity in the fibers' responsiveness (Nowlis and Frank, 1981; Hanamori et al, 1988). However, even in the face of this broad tuning, individual gustatory cells can be categorized on the basis of similarities in their response profiles and their predominant sensitivities; that is, they can be placed into functional groups (Smith et al, 1983). Attempts to understand the neural processing of taste quality information have relied heavily on this kind of classification, which depends upon the existence of four basic taste qualities: salty, sour, sweet, and bitter.

An interesting question in light of the broad tuning of taste receptor cells and first-order fibers is how any kind of code for quality can be maintained in the face of the constant turnover of receptor cells (Beidler and Smallman, 1965). Electrophysiologic work on cross-regenerated taste fibers - in which the seventh and ninth cranial nerves were cut, crossed, and allowed to reinnervate the tongue (Oakley, 1967) - demonstrated that the tongue epithelium determined the relative sensitivities of the two nerves. This was somewhat surprising, since the nerves themselves have a trophic influence over the taste buds (Guth, 1971). Nevertheless, some mechanism in the epithelium is responsible for determining the qualitative sensitivities of the taste receptors. The constant regeneration and replacement of gustatory receptor cells (Beidler and Smallman, 1965; Guth, 1971) implies that conditions that alter the structure or function of these cells, such as drugs, radiation, trace metal imbalances, or infections (Kimmelman, 1986; Schiffman, 1983a), may have only a temporary effect on taste.

The gustatory system readily adapts to constant stimulation. For example, flowing sodium chloride over the tongue for 60 seconds results in a complete disappearance of the salty sensation (Smith and McBurney, 1969). Taste receptors are particularly sensitive to changing stimuli (Smith and Bealer, 1975). Indeed, the natural course of events in tasting involves intermittent and rapid contact of the various taste buds as stimuli are moved through the oral cavity during biting, chewing, and swallowing (Halpern, 1983). Because of the rapid adaptation to constant stimulation, care must be taken in gustatory testing procedures to guard against changes in sensitivity caused by prolonged and repeated stimulation.

Physiology of Olfaction

Although most workers in taste would agree on the existence of four basic taste qualities, the situation in olfaction is much more complex. Earlier classification schemes based on the existence of "primary" odors (Amoore, 1965) have not received wide support, and there is no general agreement about odor quality classification (Engen, 1971). As a consequence of this situation, the study of olfactory physiology and behavior, unlike that of taste, has not been so strongly guided by quality labels. There are essentially hundreds of thousands of potentially effective odorants, only a fraction of which have been employed in studies of the olfactory system.

The function of the olfactory system has been studied electrophysiologically in a number of ways. A surface electrode on the olfactory epithelium records a slow, monophasic negative potential in response to odorant stimulation (Ottoson, 1956), which has been termed the *electro-olfactogram*, or EOG. These potentials are thought to be the summated generator potentials from the olfactory receptor cells (Getchell, 1974). The EOG has been a popular method for studying the electrophysiology of the olfactory receptors (Gestelend, 1971; Getchell and Shepard, 1978; Kauer, 1974). The responses of single receptor cells in the olfactory epithelium suggest that these cells are typically responsive to a wide range of stimuli (Gesteland et al, 1965). Even though a given cell responds better to some odors than to others, attempts to classify the receptors into groups on the basis of their profiles of sensitivity have not been successful (Gesteland et al, 1965; Mathews, 1972; Revial et al, 1978). However, there is some suggestion that different odorants produce different patterns of activity across the olfactory mucosa (Adrian, 1953; Kauer and Moulton, 1974; Mackay-Sim and Kubie, 1981; Mackay-Sim et al, 1982; Mozell, 1966, 1970; Mozell and Jagodowicz, 1974); that is, different regions of the olfactory epithelium give maximal responses to different odorants, as though the nose and mucosa were somehow operating like a chromatograph, separating odors on the basis of their physical and chemical properties. The measurement of radioactive odorants delivered to the nose suggests that different odors result in distinctive temporospatial patterns of sorption across the olfactory mucosa (Hornung and Mozell, 1977). Nevertheless, there is no general agreement about the way in which quality is coded by the olfactory system.

Olfactory receptor neurons are the only nerve cells known to regenerate. Even in mammals, these cells are constantly undergoing turnover (Graziadei, 1973; Monti-Graziadei and Graziadei, 1979). Cutting the olfactory nerve results in retrograde degeneration of the olfactory epithelium, which is later reconstituted from the basal cells and reconnected to the olfactory bulb (Graziadei and Monti-Graziadei, 1983). Part of the impetus for cellular turnover in the olfactory epithelium may be cellular injury from environmental exposure (Hinds et al, 1984). Thus, like taste receptor cells, olfactory neurons are in a state of constant renewal. This regenerative capacity of the olfactory epithelium provides, at least theoretically, for the possibility of recovery of function following severance of the olfactory nerve, toxic exposure, viral infection, and other conditions that may alter the structure and function of the olfactory receptor sheet.

Like taste, the olfactory response readily adapts to constant stimulation. It is well known that continual exposure to the source of an odor results in a disappearance of sensation after a short time. The response of the olfactory system is particularly sensitive to changing

stimuli (Halpern, 1983). For example, activity in the olfactory bulb is correlated very closely with the normal inhalation and exhalation cycle (Macrides, and Chorover, 1972). Because of this sensitivity to change and the rapid adaptation that occurs, care must be taken during olfactory testing to guard against changes in sensitivity that occur after prolonged and repeated stimulation.

Measurement of Taste and Smell Dysfunction

Evaluation of Taste and Smell Complaints

Although dysfunctions of taste and smell sometimes occur secondary to other disease states (Schiffman, 1983a, 1983b), their quantitative evaluation is most important when chemosensory dysfunction is the primary complaint. This evaluation must involve taking a careful medical history, with particular attention to antecedent events that might be related to the onset of the chemosensory problem (Doty, 1979; Goodspeed et al, 1987; Leopold, 1986a). The nature of the taste and smell symptoms can be a clue to the most likely cause of the problem (Gent et al, 1987). For example, if a patient with an olfactory loss reports that smell sensitivity fluctuates, it is more probable that nasal or sinus disease is involved than a previous viral infection (Gent et al, 1987). A direct question to a patient about smell loss has high predictive value; that is, nearly all patients with a diminished sense of smell will verbally report a decrease in olfactory function (Gent et al, 1987). Most patients with olfactory loss also report that they have lost the sense of taste. However, patients tend to exaggerate taste problems because of their confusion between taste and flavor. The perception of flavor involves olfactory, tactile, and thermal sensations in addition to taste, so a loss of any of these sensory modalities is usually reported as a taste loss, yielding little predictive value in such a question. Direct questions to the patient about the four qualities of taste (salty, sour, sweet, and bitter) are much more revealing of an actual taste dysfunction (Gent et al, 1987).

Dysfunctions of taste and smell can take the form of complete or partial loss of sensitivity, increased sensitivity, or a distortion of taste or smell perception. Although numerous terms have been used to classify these disorders, there is beginning to be some agreement about their usage (Doty, 1979; Kimmelman, 1986). The terms used for olfactory dysfunction include *general or total anosmia* (or, more simply, *anosmia*), which is the inability to detect any qualitative odor sensation; *partial anosmia,* which is the ability to detect some, but not all, qualitative odor sensations; *hyposmia,* which is decreased sensitivity to some or all odorants; *hyperosmia,* which is an increased sensitivity to some or all odorants; *dysosmia,* which is a distortion in the perception of a smell, such as the perception of an unpleasant odor when there is no odor present (sometimes called *phantosmia*), or the perception of an atypical odor in response to a particular stimulus (sometimes called *parosmia*); *agnosia,* which is the inability to classify, contrast, or identify an odor sensation verbally, even though the ability to distinguish between odorants or to recognize them may be normal. Somewhat similar terms are used for taste dysfunction; *ageusia,* which is the inability to detect any qualitative taste sensation; *hypogeusia,* which is a decreased sensitivity to some or all taste qualities; *hypergeusia,* which is an increased sensitivity to some or all taste qualities; *dysgeusia,* which is a distortion in the perception of taste, such as the occurrence of a persistent taste, usually unpleasant, or the perception of an atypical taste in response to a specific stimulus. Although several other terms have been used to describe taste and smell dysfunction (Henkin, 1967a; Estrum and Renner, 1987), the terms given here have

found the most common usage. However, regardless of the terminology used to classify taste and smell dysfunction, such a classification can only be as good as the procedures used to measure taste and smell function.

Psychophysical Measurement in a Clinical Setting

Much of the difficulty of dealing clinically with taste and smell complaints is in obtaining good quantitative measurements of the patient's sensory function. This difficulty is multifaceted in that this measurement must involve well-designed and standardized sensory tests and careful stimulus control and must be done in a clinical setting. No aspect of this problem is simple, and it has attracted a great deal of attention in recent years (Bartoshuk et al, 1983; Cain and Gent, 1986; Cain et al, 1983, 1988; Doty, 1979; Doty et al, 1984a; Frank et al, 1986; Gent et al, 1986; Halpern, 1986; Mozell et al, 1986; Wright, 1987). As a result, several tests have been developed and standardized on normal populations for use in the clinical testing of smell (Cain et al, 1983, 1988; Doty et al, 1984a). Taste testing has also been developed (Bartoshuk et al, 1983), but so far it lacks the standardization seen in some of the olfactory tests.

The method of presentation of olfactory and gustatory stimuli for the assessment of chemosensory dysfunction poses no small problem for the clinician. For example, controlling the concentration of an odorant is obviously an important consideration, but it is difficult to achieve. Several approaches have been taken to this problem, including the use of sniff bottles, blast injection into the nostrils, and air dilution olfactometers (Doty, 1979). One of the major considerations for clinical testing is that stimulus delivery be relatively easy and somewhat portable. Recent tests that have been developed for clinical olfactory testing (Cain et al, 1983, 1988; Doty et al, 1984a), which will be discussed at some length further on, employ the use of sniff bottles and microencapsulated ("scratch-and-sniff") odorants. Similarly, with taste, stimulus delivery can employ flowing stimuli at a fixed rate over the dorsal portion of the tongue (Smith and McBurney, 1969), having the patient sip a standard volume of stimulus (the sip-and-spit method; Bartoshuk et al, 1983), or applying solutions to different parts of the tongue and palate with filter paper or cotton swabs (Bartoshuk et al, 1983). Taste can also be stimulated electrically, and electrogustometry has been a clinical tool for some time (Frank et al, 1986). The major goal of any kind of sensory testing for taste and smell is to assess the degree of chemosensory dysfunction. Thus, many different approaches should be (and have been) employed. However, a proper assessment of chemosensory dysfunction requires the adoption of well-designed and psychophysically sound testing procedures. Such procedures have been developed within the past few years at the Connecticut Chemosensory Clinical Research Center (Bartoshuk et al, 1983; Cain et al, 1983, 1988) and the University of Pennsylvania Clinical Smell and Taste Research Center (Doty et al, 1984a). If the sensory assessment of taste and smell dysfunction could become as standard as visual or auditory assessment, the study and treatment of chemosensory disorders would greatly benefit.

Clinical Measurement of Olfaction

The clinical assessment of olfactory ability has been approached in a number of ways (Bickerstaff, 1968; Cain and Gent, 1986; Cain et al, 1983, 1988; Doty et al, 1984a; Henkin, 1981; Sumner, 1962). Traditionally, neurologists have employed odor identification to test the

sense of smell (Bickerstaff, 1968). Typically, only a few odors are used, and the response required of the patient is the identification of the odor or even a simple acknowledgment of whether the odor is smelled. Such tests are not very quantitative and also suffer from the problem that most people have difficulty identifying odors, even if they have a normal sense of smell (Cain and Gent, 1986; Doty et al, 1984a; Sumner, 1962). The ability to identify odors varies considerably across odorous substances, but even the more easily identified odors are often not easily named (Cain, 1982). Consequently, odor identification tests developed for clinical use have employed multiple-choice forms, within which persons with normal smell can show almost perfect performance (Cain et al, 1983, 1988; Doty et al, 1984a). A measurement of the confusion among odorants has also been suggested as a clinical assessment method, particularly for patients suffering from dysosmia (Wright, 1987).

Another method of assessing olfactory ability is to ask questions about a patient's detection or recognition of very weak odors, that is, to determine detection or recognition thresholds (Cain et al, 1983, 1988; Doty et al, 1986; Henkin, 1981). Threshold procedures have seen wide use in clinical studies of taste and smell (Ghorbanian et al, 1983; Henkin, 1967b; Henkin et al, 1968; Henkin and Powell, 1962; Henkin and Smith, 1971; Hertz et al, 1975; Mozell et al, 1986; Ophir et al, 1986; Weiffenback and McCarthy, 1984). An assessment of a patient's sensory threshold may provide information different from that obtained using suprathreshold (ie, magnitude scaling) procedures (Bartoshuk, 1978; Bartoshuk and Marks, 1986). For this reason, threshold procedures alone are not sufficient for chemosensory assessment.

Three tests of olfactory function that include measurements of threshold and odor identification can be employed. These tests, developed at the Connecticut Chemosensory Clinical Research Center (Cain et al, 1983, 1988) and the University of Pennsylvania Clinical Smell and Taste Research Center (Doty et al, 1984a), provide a reliable and relatively simple means of quantifying a patient's degree of olfactory functioning. The Connecticut test consists of two components: butanol threshold and odor identification. Butanol threshold (Cain et al, 1983, 1988) is assessed with a forced-choice procedure by presenting the patient with an aqueous concentration of butanol in one sniff bottle and water in the other and asking the patient to identify the bottle containing the odorant. The concentration of butanol is increased after each incorrect response (by a factor of 3) until there are five correct responses in a row or until the patient fails to correctly identify the bottle containing 4 per cent butanol. Each nostril is tested separately. The concentration step at which the patient correctly identifies the butanol on five consecutive trials is taken as the detection threshold. This step is used as a function score, which relates the patient's threshold to a normal subject population.

The odor identification test (Cain and Gent, 1986; Cain et al, 1984, 1988) consists of ten items, hidden by gauze, and presented separately to each nostril in opaque jars. These items include seven odorants (baby powder, chocolate, cinnamon, coffee, mothballs, peanut butter, and soap) and three trigeminal stimulants. The patient is given a list of 20 items, containing the ten stimuli and ten additional distractor names, from which to select a response. Feedback is given to the patient after every trial. If the patient is incorrect, a second chance is given to correctly identify the item. The number of odorants correctly identified is used as a function score, which relates the patient's performance to that of a normal control group. The performance of a patient on each of these tests is then combined in a composite function score by averaging the scores for butanol threshold and odor identification.

Frequency histograms of composite function scores for patients and controls are shown. Patients with composite scores less than 2 are considered anosmic, those between 2 and 5 are considered hyposmic, and those of 6 or greater are considered normosmic (Cain et al, 1988).

In addition to these olfactory tests, we also routinely administer the University of Pennsylvania Smell Identification Test (UPSIT), which is composed of 40 microencapsulated odors (Doty et al, 1984a). Each item of the UPSIT is presented on a "scratch-and-sniff" pad, accompanied by four response alternatives. The test is essentially self-administered, with the patient instructed to guess if unable to identify the item. Anosmic patients score at or near chance on this test, with a mean of close to 10 correct out of 40. Scores on this test have been obtained for normal individuals across a wide age range, and both sex- and age-related norms are provided. This test has been shown to have excellent short-term (r=+0.95) and long-term (r=+0.92) test-retest reliability (Doty et al, 1985). The distribution is shown of responses for anosmic individuals, normal individuals, two additional patient populations (multiple sclerosis and Korsakoff's syndrome), and normal individuals instructed to feign anosmia (cheaters). Clear separation is seen between normal individuals and those with anosmia. Also, individuals feigning anosmia tend to score much lower on the test than would be expected by chance. Extremely low scores on the UPSIT are indicative of possible malingering (Doty et al, 1984a).

There is an excellent correlation between scores on the UPSIT and the composite score of butan threshold plus odor identification across patients differing widely in olfactory ability (Smith et al, 1987). A scatterplot of the scores of 62 patients on these tests is shown. The composite scores shown are percentage scores based on an earlier version of the University of Connecticut test (Cain et al, 1983). The correlation between UPSIT scores and composite scores is +0.907. The dashed lines show the boundaries of the diagnostic categories of normosmia, hyposmia, and anosmia as defined by these two tests. A small number of patients near these boundaries (open circles in Figure 8) would be categorized differently if tested by only one method. The UPSIT scores correlated +0.925 with the odor identification scores across these 62 patients, but only +0.769 with the butanol threshold scores. The two components of the University of Connecticut battery (butanol threshold and odor identification) correlated +0.779 with one another. These assessment procedures complement and reinforce one another and provide a reliable measure of olfactory ability. In addition, the UPSIT provides age-related norms, which are useful when testing very old or very young individuals (Doty et al, 1984a).

Clinical Measurement of Taste

Although odor identification has proved to be a very useful procedure for the clinical assessment of olfactory ability, a comparable approach is not available for taste assessment, since there are essentially only four taste sensations. As a consequence, clinical assessment of taste has traditionally involved measurement of detection or recognition thresholds (Bartoshuk, 1978; Harris and Kalmus, 1949; Henkin et al, 1971). These procedures usually involve an adaptive psychophysical procedure, such as the staircase method, combined with a forced-choice procedure to ensure a bias-free measure (Bartoshuk, 1978). Threshold measures in taste, however, are subject to influences such as salivary adaptation, water tastes imparted by adaptation, or the size of the tongue area stimulated, and thus tend to be quite variable. In addition, changes in threshold do not necessarily imply changes in suprathreshold

taste intensity (Bartoshuk, 1978; Bartoshuk and Marks, 1986; Bartoshuk et al, 1983). For example, in a patient whose recognition thresholds for all four taste qualities had recovered following termination of radiation therapy, magnitude estimates of perceived intensity were still very depressed (Bartoshuk, 1978). Consequently, Bartoshuk (1978) has argued that threshold measures at their very best provide only a limited picture of sensory capacity and that assessment should be made of a patient's perceptions of suprathreshold taste intensities.

However, suprathreshold scaling has proved to be difficult to implement in the clinical situation. Standard psychophysical scaling methods require people to assign numbers to their sensations, using either direct numeric estimation of sensory magnitude or category rating scales. The major limitation of this approach for clinical assessment is that it does not allow a direct comparison across individuals. Even though two people use the same number or category to describe the intensity of a particular stimulus, they do not necessarily have equivalent experiences. What is "strong" to one individual is not the same as what is "strong" to another, nor does the number 10 or 100 have any intrinsic psychologic value (Bartoshuk et al, 1983). Thus, it is impossible to conclude that a patient is hypogeusic simply on the basis of these scale values.

This problem has been best approached through the psychophysical procedure known as magnitude matching (Bartoshuk et al, 1983; Gent et al, 1986; Marks et al, 1986; Stevens and Marks, 1980). The logic behind magnitude matching is that a deficiency in one sensory modality can be revealed if it is compared with another, presumably normal, modality on the same scale. In testing patients for taste loss, several concentrations of sodium chloride, sucrose, citric acid, and quinine hydrochloride and several loudness levels of a 1000-Hz tone have been used for this magnitude matching task (Bartoshuk et al, 1983; Gent et al, 1986). The taste solutions are presented in medicine cups, which the patient sips and then expectorates, and the tones are presented through headphones. Patients are asked to provide estimates of perceived magnitude for all of these stimuli, which are presented randomly. The psychophysical functions for taste are then scaled in relation to the loudness functions (which are presumed to be normal). Abnormalities of taste are then revealed as depressed psychophysical functions, with hypogeusic patients associating strong taste concentrations with the weaker tones. Given patients with normal hearing, this procedure works well to provide an absolute measure of taste loss. Its major limitations are the dependence upon normal hearing, which can sometimes be a problem for elderly individuals, and its relatively complicated design, which requires considerable time to run and analyze. Studies are currently under way in an effort to make this procedure more adaptable to the clinic (Stone et al, 1987).

Because the gustatory system is multiply innervated by three cranial nerves, it is relatively resistant to traumatic destruction in comparison with the olfactory system. Occasionally, however, patients present with potential damage to one or more of these gustatory nerves. The degree of taste function in the various areas of the tongue and oral cavity can be assessed using a spatial test (Bartoshuk et al, 1983; Gent et al, 1986; Goto et al, 1983). In this test, strong concentrations of the four basic tastes are randomly placed on the four quadrants of the tongue (left and right front edges and back edges) and on the soft palate bilaterally. Stimuli can be delivered with filter paper soaked in the solution and placed on the tongue or palate (Bartoshuk et al, 1983; Gent et al, 1986) or by cotton-tipped applicators. Patients are asked to identify the quality of the taste and to rate its intensity using the same scale as in the whole mouth assessment. This test is useful in assessing taste loss

caused by a pathologic condition of the chorda tympani, of the glossopharyngeal or greater superficial petrosal nerves, or of their ganglia. The clinical assessment of taste function is not as well developed as that of olfaction. This development awaits the accumulation of normative data of the sort available for the olfactory tests and is also dependent upon continuing efforts to improve the testing procedures.

Patients with Primary Chemosensory Complaints

Frequent Causes of Olfactory Dysfunction

Olfactory and taste dysfunction have been associated with a number of systemic diseases and metabolic disorders (Doty, 1979; Doty and Kimmelman, 1986; Doty and Snow, 1987; Estrum and Renner, 1987; Feldman et al, 1986; Henkin, 1981; Kimmelman, 1987; Leopold, 1986a; Schiffman, 1983a, 1983b). However, most patients presenting with a primary complaint of taste or smell dysfunction fall into only a few diagnostic categories. Of 441 patients presenting to the Connecticut Chemosensory Clinical Research center, most (85.4 per cent) complained of a reduced ability to smell, and more than half (59.8 per cent) complained of a reduced ability to taste (Goodspeed et al, 1987). Dysosmias, either parosmias or phantosmias, were reported by 19.3 per cent of these patients, and persistent unpleasant tastes were reported by 17.5 per cent of the patients. Measurement of chemosensory capacity in these patients revealed that 86 per cent had olfactory deficits, but only 30 per cent had a measurable taste deficit. Thus, patients quite accurately report loss of smell but are not so accurate in their reports of taste dysfunction (Gent et al, 1987). This discrepancy reflects the common confusion between taste (ie, salty, sweet, sour, and bitter) and flavor (which includes taste, smell, texture, and temperature). Similar results have been reported on a smaller number of patients at the University of Cincinnati Taste and Smell Center (Smith et al, 1987).

Patients with a primary olfactory complaint most likely fall into one of four etiologic categories: (1) nasal or sinus disease, or both (ie, nasal polyposis, chronic sinusitis, allergic rhinitis, and so forth); (2) prior upper respiratory infection (ie, a history of a viral-like upper respiratory illness just prior to the onset of the olfactory loss); (3) idiopathic causes; or (4) head trauma (Goodspeed et al, 1987; Henkin, 1981; Smith et al, 1987). These four categories account for 83 per cent (Goodspeed et al, 1987), 72 per cent (Henkin, 1981), 85 per cent (Smith et al, 1987), and 82 per cent (Doty, personal communication), respectively, of olfactory deficits in patients presenting with primary chemosensory complaints at four different centers. The terminology in the literature is somewhat different, with Henkin's (1981) postinfluenza hyposmia and hypogeusia (PIHH) and allergic rhinitis categories corresponding to what is referred to here as prior upper respiratory infection and nasal or sinus disease, respectively. In the three largest studies, the most frequent cause of olfactory dysfunction was nasal or sinus disease (Goodspeed et al, 1987) or prior upper respiratory infection (Doty, personal communication; Henkin, 1981). This difference probably reflects the nature of the referral patterns to these centers. Since the Connecticut group (Goodspeed et al, 1987) sees mostly self-referred patients, those with nasal disease are much more likely to appear than if they were referred by other physicians. Nevertheless, the great majority of patients with olfactory complaints falls into one of these four etiologic categories. In addition to these major causes of smell dysfunction, smaller numbers of patients who present with primary olfactory complaints have impairment caused by exposure to toxic chemicals, craniofacial surgery, seizure disorders, cerebrovascular accidents, endocrine disorders, congenital causes,

or other conditions (Feldman et al, 1986; Goodspeed et al, 1987; Henkin, 1981; Smith et al, 1987). Relatively few patients present with primary chemosensory complaints resulting from the many widespread systemic or metabolic diseases (Schiffman, 1983a, 1983b) claimed to be responsible for taste or smell dysfunction (Goodspeed et al, 1987).

Nasal and Sinus Disease

Olfactory disorders can be characterized as (1) conductive disorders, arising from interference with the access of odorants to the olfactory receptors or (2) sensorineural disorders, resulting from damage to the receptors or olfactory pathways (Doty and Snow, 1987). Unfortunately, olfactory testing alone is not capable of distinguishing between these possibilities. Of the four major etiologic categories, only nasal or sinus disease typically involves a conductive loss, which results from the restriction of upper airway patency. This obstruction may arise from intranasal polyposis, chronic sinusitis, or allergic rhinitis. The loss of smell resulting from nasal and/or sinus disease is usually quite severe, with most patients characterized as anosmic (about 75 per cent) rather than hyposmic (Goodspeed et al, 1986a, 1987; Smith et al, 1987). Even a moderate degree of ostiomeatal disease without accompanying polyps can result in significant olfactory impairment (Seiden and Smith, 1988). In one study, about one-third of patients with IgE-mediated nasal allergy were shown to have a measurable olfactory impairment (Seiden et al, 1989), the deficit being worse in patients with nasal polyps. The fact that a conductive loss is often involved in this condition is demonstrated by the fact that patients with nasal or sinus disease are much more likely to verbally report fluctuations in smell sensitivity than are those with loss due to a prior upper respiratory illness (Gent et al, 1987); that is, these patients sometimes have a temporary return in their sense of smell, often associated with exercise or medications. Anosmic patients with allergic rhinitis or nasal polyposis, or both, have been shown to recover olfactory function following administration of systemic corticosteroids (Fein et al, 1966; Goodspeed et al, 1986b; Hotckiss, 1956) or after careful intranasal administration of topical corticosteroids (Scott et al, 1988). Although chronic administration of systemic steroids is not a recommended treatment for anosmia, a short course of steroid therapy may help in diagnosing nasal disease as the cause of the olfactory loss (Leopold, 1986a). Surgical procedures that reduce nasal obstruction have also been shown to produce marked improvement in olfactory sensitivity (Ghorbanian et al, 1983; Ophir et al, 1986). Endoscopic ethmoidectomy to alleviate allergic disease in the ostiomeatal complex has been shown to restore olfactory sensitivity, with some patients maintaining this improvement for as long as 1.5 to 2 years, even without concomitant steroids or immunotherapy (Seiden and Smith, 1988). Thus, olfactory losses resulting from an interference with odor access to the receptors - that is, conductive losses - are often amenable to treatment (Doty and Snow, 1987).

Prior Upper Respiratory Infection

Olfactory losses with sensorineural involvement are more difficult to manage at present than are those resulting from conductive disorders. Anosmia or hyposmia following a viral-like upper respiratory infection may be of the sensorineural type, although the exact pathogenesis of this condition is currently unknown. The diagnosis of postviral anosmia or hyposmia rests primarily on the coincidence of a viral illness or cold just prior to the onset of olfactory loss along with a lack of other causative factors (Goodspeed et al, 1987). Some investigators, however, have suggested that there are characteristic changes in the nasal

mucosa in this condition (Henkin et al, 1975). An earlier biopsy study suggested that the olfactory epithelium in postviral anosmia may be damaged, with extensive scarring and replacement of the olfactory epithelium with respiratory epithelium (Douek et al, 1975). These data also suggested that stem cells are still present, holding out hope for regeneration of the olfactory epithelium. However, this information comes from biopsy of a single patient, and much more extensive ultrastructural studies are needed (Jafek, 1983; Lovell et al, 1982). A more recent ultrastructural study of the human olfactory epithelium demonstrated a loss of olfactory receptor cells and an absence of olfactory cilia on the remaining receptors in patients with viral-induced smell loss (Jafek and Eller, 1989). Influenza viruses are known to affect ciliary activity in the respiratory epithelium and to produce necrosis of pseudostratified ciliated columnar epithelium (Snow, 1969); thus, similar processes could be acting on the olfactory neuroepithelium (Doty, 1979). In addition, the olfactory epithelium has been shown to be a route of viral invasion of the central nervous system (Monath et al, 1983). Thus, the long-lasting effects of a viral illness could be the result of damage to the olfactory epithelium or could even involve central olfactory mechanisms.

In comparison with patients having nasal or sinus disease, those with smell dysfunction following an upper respiratory infection are more likely to be women, older, hyposmic rather than anosmic, and to also show some hypogeusia (Goodspeed et al, 1987). Patients with these types of diseases (nasal disease or postviral anosmia) often report parosmias or phantosmias, almost always of an unpleasant nature (Smith et al, 1987). Although it has sometimes been suggested that postviral anosmia may show spontaneous remission (Goodspeed et al, 1986a), there is no hard evidence to support such a claim. Similarly, there is no evidence to support the suggestion that these patients are unlikely to ever recover (Marshall and Attia, 1987). Patients in this category have been seen from a few months to several years following the onset of their olfactory loss, but there have been no systematic follow-up procedures nor any attempt to correlate the degree of olfactory loss with the time of onset. Thus, the mechanism of viral-induced anosmia is unknown, and the prognosis for this disorder is completely uncertain. Given the relative frequency of this etiologic presentation in the production of olfactory loss, further research on the mechanisms and time course of postviral anosmia is sorely needed.

Head Trauma

About 5 per cent of patients with head injury suffer a resulting olfactory loss (Leigh, 1943; Sumner, 1964; Zusho, 1982; Constanzo and Becker, 1986), and these patients make up about 10 to 20 per cent of those presenting with primary olfactory complaints (Goodspeed et al, 1987; Henkin, 1981; Smith et al, 1987). The loss of smell sensitivity following head trauma is sometimes accompanied by dysosmia, involving unpleasant smell sensations (Costanzo and Becker, 1986; Schechter and Henkin, 1974; Leigh, 1943), although there is some indication that dysosmias may be less frequent in patients with head injury than in those with nasal disease or viral causes (Smith et al, 1987). As in patients with nasal or sinus disease, olfactory impairment in patients with head injury is more likely to be severe, with a much greater percentage (about 80 per cent) showing anosmia than hyposmia (Goodspeed et al, 1986a; Smith et al, 1987). Post-traumatic anosmia is commonly thought to result from shearing of the olfactory nerve filaments or from contusions following a sudden blow to the head (Costanzo and Becker, 1986). In laboratory animals, intracranial hemorrhage and cerebral ischemia have also been shown to lead to degeneration of the olfactory epithelium,

even though the olfactory nerve is intact (Nakashima et al, 1983, 1984a). Thus, a number of mechanisms may be involved in olfactory dysfunction following head trauma.

Since the olfactory system is remarkable in its ability to regenerate (Graziadei, 1973; Graziadei and Monti-Graziadei, 1983), there is the potential for recovery of olfactory function after head injury. Indeed, recovery of the olfactory neuroepithelium is typically seen in laboratory animals following olfactory axotomy (Monti-Graziadei and Graziadei, 1979; Monti-Graziadei et al, 1980; Simmons and Getchell, 1981). In addition, recordings from cells in the hamster olfactory bulb demonstrate functional recovery within 9 months following olfactory nerve transection (Costanzo, 1985). However, the prognosis for the recovery of smell in humans after traumatic injury is generally poor, with various estimates of 15 per cent (Zusho, 1982), 33 per cent (Costanzo and Becker, 1986), and 39 per cent (Sumner, 1964). The time course for recovery is also somewhat questionable, with about 80 per cent of recovery occurring within 6 months in one study (Sumner, 1964) but only after about 20 months in another study (Costanzo and Becker, 1986). These differences may reflect the way in which olfactory function was measured in these studies, as well as the criteria for recovery. Nonetheless, recovery from post-traumatic anosmia may proceed over a period as long as 5 years (Costanzo and Becker, 1986; Sumner, 1964). It has been suggested that early recovery may be due to mechanisms such as the disappearance of blood clots or edema and that the later recovery may reflect the regeneration of neural elements (Sumner, 1975). Further research is needed delineate these mechanisms. Some patients may experience parosmia or phantosmia during the recovery process (Goodspeed et al, 1986a; Leigh, 1943), although the mechanisms for these phenomena are unknown. It has been suggested that the occurrence of parosmia may reflect a system that is minimally functional (Wright, 1987). Consistent with this hypothesis is the fact that patients with head injury who report parosmia or phantosmia score significantly higher on the UPSIT than do those without these symptoms (Smith et al, 1987).

Idiopathic Smell Dysfunction

A large group of patients with primary olfactory complaints does not fall easily into any diagnostic category, and the cause of the loss of smell remains unknown. The cause in these patients has been termed *idiopathic,* and these patients compose 17.9 per cent (Smith et al, 1987), 19 per cent (Henkin, 1981), and 25.9 per cent (Goodspeed et al, 1987) of those with olfactory dysfunction in different studies. Although a specific syndrome of idiopathic hypogeusia and hyposmia, with or without dysgeusia and dysosmia, has been described (Henkin et al, 1971), this categorization appears to reflect cases for which no specific cause can be established (Goodspeed et al, 1987). Many of these patients may have olfactory symptoms as a result of one of a vast number of systemic diseases or neurologic or endocrine disorders (Doty, 1979; Feldman et al, 1986; Jafek, 1982; Kimmelman, 1986; Schiffman, 1983a, 1983b) that are not being detected during the olfactory evaluation. As our ability to provide a differential diagnosis for the cause of olfactory dysfunction improves, the number of patients with idiopathic olfactory disturbances will probably decrease (Feldman et al, 1986; Gent et al, 1987; Liston, 1984).

Other Causes

Most patients (about 80 per cent) presenting with primary olfactory complaints will fall into one of the four etiologic categories described previously. The remaining patients are diagnosed with one of several other causes. For example, in the study reported by Goodspeed and co-workers (1987), an additional 4.5 per cent of their patients were considered to have multiple causes, such as a patient with a temporally related head trauma who also experienced a viral-like upper respiratory infection at about the same time. For these patients, the establishment of one definitive cause for their olfactory loss was impossible (Goodspeed et al, 1987). In several studies, small numbers of patients (5 to 14 per cent) have been grouped into a miscellaneous category, which reflects diverse causes, such as seizure disorders, cerebrovascular accidents, brain surgery, endocrine disorders, and depression (Goodspeed et al, 1987; Henkin, 1981; Smith et al, 1987).

A few patients (1 to 2 per cent) present with primary olfactory complaints stemming from exposure to toxic chemicals (Goodspeed et al, 1987; Henkin, 1981; Smith et al, 1987). A number of environmental and industrial pollutants have been implicated in anosmia or hyposmia, including benzene, benzol, butyl acetate, carbon disulfide, ethyl acetate, formaldehyde, hydrazine, menthol, paint solvents, oil of peppermint, trichlorethylene, and a variety of industrial dusts such as cadmium and nickel (Amoore, 1986; Doty, 1979; Halpern, 1985). As Doty (1979) has pointed out, many of the studies implicating these various chemicals in olfactory dysfunction suffer from methodologic problems, so it is hard to draw any general conclusions from these data. However, in one well-controlled study, 27.3 per cent of workers in an alkaline battery plant who were exposed to high levels of cadmium were found to by hyposmic or anosmic, compared with 4.8 per cent of control subjects from a neighboring nonchemical factory (Adams and Crabtree, 1961). Experimental studies demonstrate that a 1 per cent solution of zinc sulfate will destroy the receptor cells and supporting cells of the olfactory epithelium of mice (Cancalon, 1982). Recovery of the receptor cells and olfactory cilia is seen in 4 to 6 weeks after zinc sulfate treatment. Similarly, cigarette smoke has been shown to alter the ultrastructure of the olfactory epithelium in certain strains of mice, resulting in, among other changes, reduced or lacing olfactory cilia (Matulionis, 1974). Although there has been relatively little work in this area, there is some suggestion that smoking results in decreased olfactory sensitivity (Hubert et al, 1980; Thumfart et al, 1980; Venstrom and Amoore, 1968). However, other investigators have found no effect of smoking on olfactory sensitivity, but have shown a clear reduction in the perception of nasal pungency, mediated through the trigeminal system (Cain, 1981; Cometto-Muniz and Cain, 1982; Dunn et al, 1982). More studies of the effects of environmental pollutants on olfactory sensitivity are needed to clearly establish those that might be implicated in patients presenting with a history of toxic exposure.

Frequent Causes of Gustatory Dysfunction

Of those patients presenting with primary chemosensory complaints, more than half claim to have a reduced sense of taste (Goodspeed et al, 1987). However, measurable gustatory dysfunction is seen in less than one third of all patients (Goodspeed et al, 1987; Smith et al, 1987). This discrepancy arises because of the common confusion between taste and flavor (as discussed previously), which causes patients with olfactory loss to ascribe their impaired flavor perception to a gustatory loss (Henkin, 1981). Measured gustatory impairment

usually involves hypogeusia or dysgeusia. Total loss of taste (ageusia) is very rare (Goodspeed et al, 1987). Taste dysfunction often accompanies olfactory loss and is less common as an isolated entity (Goodspeed et al, 1986a). Of 67 patients presenting to the University of Cincinnati Taste and Smell Center, 22 had measurable taste loss (Smith et al, 1987). Of these 22 patients, the gustatory loss was attributable to head injury (27.3 per cent), prior upper respiratory infection (13.6 per cent), idiopathic causes (13.6 per cent), toxic exposure (9.1 per cent), peripheral nerve damage (9.1 per cent), and several other causes (18.2 per cent), including cerebrovascular accident and medications. Thus, except for nasal or sinus disease, the most frequent causes of taste dysfunction are the same as for olfactory dysfunction (prior upper respiratory infection, head injury, and idiopathic causes). Taste losses have been reported previously for patients with head injury (Costanzo and Becker, 1986; Goodspeed et al, 1986a; Schechter and Henkin, 1974; Sumner, 1975) or prior upper respiratory infection (Goodspeed et al, 1986a; Henkin et al, 1975). In addition, a specific syndrome of idiopathic hypogeusia with dysgeusia, hyposmia, and dysosmia has been described (Henkin et al, 1971), although such a classification may simply reflect our inability to identify the cause in many instances of taste loss.

One of the most troublesome conditions that is relatively common in patients presenting to a taste and smell clinic is dysgeusia, that is, the presence of a persistent, usually unpleasant, taste. Of 67 patients presenting to the University of Cincinnati Taste and Smell Center with chemosensory complaints, 8 complained of the constant presence of a persistent taste (Smith et al, 1987). Four of these patients were considered to have idiopathic disease and three of these four patients reported a strong and persistent salty sensation. Dysgeusia in the other four patients was associated with nerve damage, toxic exposure, stroke, or head trauma (Smith et al, 1987). Dysgeusias have been reported to occur i patients with poor oral hygiene (Langan and Yearick, 1976) and in those with glossitis due to *Trichomonas* infection (Brenner and Simon, 1984). Patients with burning mouth syndrome often experience dysgeusia and hypogeusia in addition to pain (Grushka et al, 1986). Gustatory loss or dysgeusia, or both, have been reported to occur following administration of a number of drugs (Johnson et al, 1986; Rollin, 1978) or after parenteral chemotherapy (Fetting et al, 1985). Dysgeusia following drug treatment are often caused by the presence of detectable levels of the drug in the saliva or by a drug-induced xerostomia. It is also possible for patients to taste some substances present in the blood if the concentrations are sufficient for intravascular taste (Bradley, 1973). In general, the effects of pharmacologic agents on taste and smell are thought to be due to either a disturbance in the normal turnover of receptors or a chronic change in their local environment (Schiffman, 1983a). In the evaluation of patients with dysgeusia, particular attention should be given to their oral and dental health and to the medications they are currently taking, as these are the most common known causes of persistent tastes.

As was seen for olfaction, a number of environmental influences can also alter taste sensitivity. Taste loss has been reported in patients undergoing radiation treatment for head and neck cancer (Conger, 1973; Kalmus and Farnsworth, 1959; Mossman and Henkin, 1978; Mossman, 1986). This decrease in taste acuity, which normally recovers within 2 to 4 months after radiation therapy is discontinued, is thought to be due to radiation-induced damage to the microvilli of the taste receptor cells (Conger, 1973; Conger and Wells, 1969). The influence of smoking on the sense of taste is controversial. Some studies suggest that taste sensitivity is decreased in smokers, but the effect is not a large one (Coats, 1974; Jackson, 1967; Kaplan et al, 1964; Krut et al, 1961; Peterson et al, 1968). Others see no difference

between smokers and nonsmokers (Pangborn and Trabue, 1973). There are large methodologic differences among these studies, suggesting that this question needs to be re-examined with careful psychophysical methods, including suprathreshold procedures such as magnitude matching. There does seem to be some agreement on the effects of smoking on taste and food preferences, in which it is suggested that smokers increase their preferences for sweet substances when they stop smoking (Grunberg, 1982; Wynder et al, 1967) or that smokers prefer stronger tasting foods (Perrin et al, 1961). However, it is not at all clear how these preference data relate to the question of gustatory sensitivity. There have been no indications that any primary complaints of taste or smell loss by patients presenting to a taste and smell clinic are attributable to smoking (Goodspeed et al, 1986a, 1987; Henkin, 1981; Smith et al, 1987).

Taste and Smell in Aging and Disease

Aging and the Chemical Senses

There are many studies suggesting a decline in chemosensory ability to humans with increasing age (Doty et al, 1984b; Doty and Snow, 1988; Murphy, 1986; Schiffman, 1979; Stevens et al, 1984; Van Toller et al, 1985; Weiffenbach et al, 1986). Olfactory thresholds have been shown to decrease in old age (Cain et al, 1987; Deems and Doty, 1987; Murphy, 1983; Thumfart et al, 1980; Venstrum and Amoore, 1968). Van Toller and colleagues (1985) have shown significant declines in olfactory thresholds with age across ten different odorants for individuals between the ages of 20 and 80 years. In addition to changes in detectability, the perception of suprathreshold odors also appears to decline with increasing age. This decline is clearly evident in estimates of perceived odor intensity measured with magnitude matching procedures (Stevens and Cain, 1985; Stevens et al, 1982, 1984) as well as in the ability to identify odors (Doty et al, 1984b; Murphy, 1986). The variation in performance on the UPSIT as a function of age and sex is shown (Doty et al, 1984b). Although females are slightly better at identifying odors than are males at all ages, there is a sharp decline in the performance of both sexes after the age of 69 years. Also evident in this figure is an increase in the variance of the scores at older ages, which suggests that some older individuals show considerably more impairment than others. However, after the age of 80 years, more than 80 per cent of the persons tested showed major olfactory impairment, with nearly 50 per cent being anosmic (Doty et al, 1984b). This impairment in odor identification parallels that seen using threshold techniques (Cain et al, 1987; Deems and Doty, 1987). Thus, both the absolute sensitivity to odor and the appreciation of strong suprathreshold odors show a decrement with increasing age. These data help to explain why many elderly persons complain about a lack of flavor in their food (Cohen and Gitman, 1959) and have difficulty detecting life-threatening fires and gas leaks (Cain and Turk, 1985; Doty et al, 1984b).

There is a relatively greater loss in olfactory ability with age than in gustatory ability (Stevens et al, 1984). Although there appear to be elevations in taste thresholds in elderly individuals (Grzegorczyk et al, 1979; Moore et al, 1982; Murphy, 1979; Schiffman et al, 1979; Weiffenbach et al, 1982), the perception of strong tastes does not appear to be greatly impaired by aging (Bartoshuk et al, 1986; Stevens et al, 1984). Using the technique of magnitude matching, in which taste sensations are compared directly with auditory sensations, Bartoshuk and colleagues (1986) showed that weak tastes were matched to louder sounds by elderly (but normal-hearing) subjects (aged 74 to 93 years), but that strong tastes were judged

to be similarly strong by elderly and young (aged 20 to 30) individuals. The magnitude matching function for sucrose is shown, and it may be seen that the psychophysical function for elderly individuals is flatter than for younger subjects and that the estimates of the stronger sucrose solutions were the same for both groups (Bartoshuk et al, 1986). A similar flattening of the magnitude functions for taste with age has been reported by a number of investigators (Schiffman and Clark, 1980; Schiffman et al, 1981; Weiffenbach et al, 1986). This increase at the weaker concentrations was seen for all qualities and was attributed to the presence of dysgeusia in the older subjects (Shafar, 1965), which added to the taste stimuli (Bartoshuk et al, 1986). This interpretation is consistent with the increase in detection thresholds with age that are also reported by these authors and by others (Bartoshuk et al, 1986; Grzegorczyk et al, 1979; Moore et al, 1982; Murphy, 1979; Schiffman et al, 1979; Weiffenbach et al, 1982). Thus, unlike the marked decline in olfactory sensitivity seen at both threshold and suprathreshold intensities, age appears to affect taste only at threshold levels, and this may be due to the presence of a chronic masking taste in the mouths of elderly individuals. The fact that this dysgeusia may reflect underlying dental problems is suggested by the reduction in taste thresholds reported in elderly individuals with improved oral hygiene (Hyde et al, 1981; Langan and Yearick, 1976). As a final word of caution, it is obvious that age-associated deficits on a sensory task may reflect factors other than sensory loss (Weiffenbach, 1984). The magnitude matching procedure, which requires subjects to assess both auditory and taste or olfactory stimuli simultaneously, along with a careful assessment of the cognitive status of elderly subjects, provides a good tool for the study of the sensory effects of aging (Marks and Stevens, 1980; Stevens and Marks, 1980).

These relatively small changes seen in gustatory function in human adults are paralleled by anatomic studies of taste buds in rodents (Mistretta and Baum, 1984), primates (Bradley et al, 1985), and humans (Arvidson, 1979), which show no decrease in taste bud number as a function of age. These recent data contradict several earlier reports of decreasing numbers of taste buds in older individuals. Neurophysiologic studies on aging rats suggest very minor changes in taste responses of the chorda tympani nerve, reflected only in the relative responses among some stimuli (Mistretta, 1984). In contrast to this relative lack of age-related changes in the gustatory system, the olfactory system shows some fairly marked changes with age (Mistretta, 1984). The number of receptor cells in the olfactory epithelium overlying the nasal septum in the rat is seen to initially increase with age, up to about 18 months, and then to show a gradual, and finally a rapid, decrease in old age, after about 30 months (Hinds and McNelly, 1981). Laging about 3.5 months behind this decrease in the number of receptor cells is a parallel decrease in the size of second-order mitral cells in the olfactory bulb (Hinds and McNelly, 1981). In humans, examination of autopsy material has shown a marked degeneration of receptors cells in the olfactory neuroepithelium with increasing age (Nakashima et al, 1984b), as well as decreases in the number of glomeruli in the olfactory bulb, which indicates a decrement in the number of olfactory nerve fibers with age (Smith, 1942). Although there are these well-documented changes in the olfactory system of aged rats and humans, it is not clear how these particular changes affect olfactory acuity (Mistretta, 1984). Nevertheless, psychophysical data from human studies and anatomic data from humans and several other mammalian species suggest that age has a more profound effect on the olfactory system than on the gustatory system.

Taste and Smell Dysfunction Secondary to Other Diseases

Disorders of taste and smell have been associated with a number of conditions, including endocrine, neurologic, psychiatric, and nutritional disorders (Doty, 1979; Doty and Kimmelman, 1986; Doty and Snow, 1987; Estrum and Renner, 1987; Feldman et al, 1986; Henkin, 1981; Kimmelman, 1986; Leopold, 1986a; Schiffman, 1983a, 1983b). Although the occurrence of these disorders in patients presenting with primary taste or smell complaints is relatively rare, these conditions must always be considered in the evaluation of these patients. Disorders that have been reported to affect the senses of smell and taste are listed in Tables 1 and 2, which categorize them into endocrine disorders, neurologic disorders, nutritional disorders, local diseases or mechanical obstruction, psychiatric disorders, tumors, and infectious processes. Listed with each of these categories is a reference, which reflects either a research study demonstrating the association of that particular factor with an olfactory or taste disturbance or a review article covering a wide range of studies. The article by Amoore (1986) on the effects of chemical exposure on olfaction is an example of the latter. Some of these conditions were discussed previously as common causes of olfactory or taste impairment seen in patients with primary chemosensory complaints. Others represent relationships described in the literature but uncommon in patients presenting primarily with taste or smell symptoms (Goodspeed et al, 1987). Because many of these studies have measured only thresholds, which alone do not provide a complete picture of a patient's sensory impairment (Bartoshuk, 1978; Bartoshuk and Marks, 1986), these relationships must be carefully evaluated. Some of the earlier studies involved only a patient's subjective report of taste or smell symptoms and are even less reliable than those reporting the results of threshold testing. In many cases, for example, cystic fibrosis, earlier reports (Henkin and Powell, 1962) have been cotraindicated by more recent studies (Hertz et al, 1975; Weiffenbach and McCarty, 1984).

A number of endocrine disorders have been reported to influence taste and smell function. Olfactory impairment is seen in several kinds of gonadal dysfunction. Patients with hypogonadotrophic hypogonadism (Kallmann's syndrome) often exhibit a congenital anosmia (Kallmann et al, 1944), which has been shown to follow an autosomal dominant mode of inheritance with incomplete expressivity (Santen and Paulsen, 1973). Although Kallmann's syndrome usually occurs in men, some women with hypogonadotrophic hypogonadism have also been described as anosmic (Tagatz et al, 1970), as have those with primary amenorrhea (Marshall and Henkin, 1971). Patients with chromatin-negative gonadal dysgenesis (Turner's syndrome) have been reported to have both taste and smell impairment (Henkin, 1967c). Changes in smell sensitivity also occur during the human menstrual cycle, with peaks in sensitivity in midcycle, during the midluteal phase, and sometimes in the latter part of the menses (Doty et al, 1981). Since these changes are also seen in women on oral contraceptives, it is not clear whether these fluctuations are modulated by gonadal hormones or are solely under the control of central neural factors (Doty, 1979; Schneider et al, 1958). Disorders of thyroid or parathyroid function have been associated with both taste and smell impairment. Patients with untreated primary hypothyroidism have been shown to have elevated taste and smell thresholds, which return to normal after treatment with thyroxine (McConnell et al, 1975). Suprathreshold intensities of salty and bitter stimuli are also rated less strong by patients with early hypothyroidism, and this effect is reversed by thyroid hormone treatment (Mattes et al, 1986). Pseudohypoparathyroidism, which is characterized by a lack of response to parathyroid hormone, has been associated with increased smell thresholds and decreased

sensitivity to sour and bitter tastes (Henkin, 1968). Chemosensory impairment has also been related to adrenocortical function. The hyperadrenocorticism characteristic of Cushing's syndrome has been associated with increases in both taste and smell thresholds, whereas decreased detection thresholds for both taste and smell have been shown in patients with adrenocortical insufficiency (Henkin, 1975). Finally, taste and smell sensitivity appear to be reduced in some patients with diabetes mellitus (Settle, 1986). Some of this impairment is due to the effects of diabetic neuropathy (Abbasi, 1981), but a general deficit in taste sensitivity to glucose is seen in patients with noninsulin-dependent diabetes and in their close relatives (Lawson et al, 1979). Patients with asymptomatic diabetes also have reduced taste sensitivity to glucose (Schelling et al, 1965). Thus, taste or smell impairment, or both, have been suggested in a number of endocrine disorders, any of which could be of etiologic significance inpatients with taste and smell complaints.

Olfactory and taste dysfunctions are sometimes observed in patients with several types of neurologic impairment. Head trauma was already discussed as one of the major etiologic factors in patients with primary chemosensory complaints. When neurologic disease involves peripheral or central chemosensory pathways, taste and smell function can be compromised. For example, taste impairment has been seen in Bell's palsy when it involves the chorda tympani branch of the seventh cranial nerve (Ekstrand, 1979). Two patients were seen at the University of Cincinnati Taste and Smell center with unilateral ageusia following surgical damage to the seven cranial nerve, in which the taste loss was limited to the anterior portion of the tongue ipsilateral to the nerve damage. Similarly, patients surviving a tegmental type of primary pontine hemorrhage have been shown to be ageusic or hypogeusic for all taste qualities on the front and rear portions of the tongue and on the soft palate on the side ipsilateral to the pontine lesion as a result of the disruption of ascending fibers from the solitary nucleus (Goto et al, 1983). Demonstration of these kinds of taste impairment involving only a limited portion of the gustatory system requires spatial testing, in which stimuli are placed on the four quadrants of the tongue and on the soft palate bilaterally (Bartoshuk et al, 1983; Gent et al, 1986; Goto et al, 1983). Generally, patients with spatial damage appear normal on whole mouth taste tests because of spatial summation from the remaining intact taste buds. Both taste and smell dysfunction have been reported for patients with familial dysautonomia, which is characterized by a complete lack of lingual taste buds (Henkin and Kopin, 1964). These patients have elevated thresholds (or complete ageusia) for all taste qualities, which were reported to return to normal after subcutaneous administration of methacholine. These authors attributed this cholinergic effect to taste transduction via free nerve endings, since these patients were without taste receptors (Henkin and Kopin, 1964). These findings are difficult to interpret, as is the reduced smell sensitivity to thiophene and pyridine seen in some of these patients (Henkin and Kopin, 1964). The demyelinating effects of multiple sclerosis have been shown to produce deficits in taste and perhaps in smell (Catalanotto et al, 1986; Cohen, 1965; Doty et al, 1984a; Pinching, 1977; Wender and Szemza, 1971). Small numbers of multiple sclerosis patients have been reported to have taste impairment. Electrogustometric testing of multiple sclerosis patients showed 4 of 52 individuals with taste deficits in one study (Wender and Szemza, 1971) and 4 of 90 patients with taste deficits in another (Rollin, 1976). A recent study of 79 patients with multiple sclerosis has shown significant decrements in the perceived intensity of sodium chloride and quinine hydrochloride solutions (Catalanotto et al, 1986), although these effects were small and were not obtained with magnitude matching procedures. Comparisons across groups of subjects require some kind of normalization procedure to equalize the ratings of the two

groups (Bartoshuk et al, 1983). These investigators (Catalanotto et al, 1986) matched the multiple sclerosis patients to controls by equating their responses to 1.0 M sucrose, which would tend to eliminate any differences in perceived sweetness between the two groups. Therefore, it is difficult to argue that multiple sclerosis only affects the perception of saltiness and bitterness. Although there does seem to be some kind of taste impairment in these patients, further work is needed to clarify the details of these deficits. Even greater questions arise regarding olfactory deficits in multiple sclerosis. Early work in this area is conflicting, with some studies (measuring odor identification) suggesting olfactory impairment (Wender and Szemza, 1971) and others (measuring detection thresholds) suggesting no deficit at all (Ansari, 1976). These differences may reflect the effects of multiple sclerosis on the higher cognitive functions involved in odor identification (Pinching, 1977), although recent work with the UPSIT (Doty et al, 1984a) shows only a small number of multiple sclerosis patients with smell impairment. Thus, taste and smell may be compromised by multiple sclerosis in some patients, probably depending upon the particular distribution of the disease.

Recent works has shown that a number of central neural disorders seem to involve olfactory deficits, including epilepsy (Eskenazi et al, 1986), Parkinson's disease (Ansari and Johnson, 1975; Doty and Snow, 1988; Quinn et al, 1987; Ward et al, 1983), and Alzheimer's disease (Doty et al, 1987; Serby, 1986). Patients with temporal lobe epilepsy are slightly deficient in odor identification and odor recognition memory, and these deficiencies are exacerbated by temporal lobectomy, with greater impairment for the nostril ipsilateral to the lesion (Eskenazi et al, 1986). There does not appear to be any difference between normal controls and epileptic patients in butanol threshold tests (Eskenazi et al, 1986). Since these patients were also deficient in recognition memory for amorphous shapes, these impairments may have more to do with odor memory processing than with sensory impairment. Several studies suggest that patients with Parkinson's disease show deficits in olfactory ability. Early work by Ansari and Johnson (1975) demonstrated that 10 to 22 parkinsonian patients had increased thresholds for amyl acetate. This deficit was confirmed by Ward and co-workers (1983) using an odor identification test, in which 49 per cent of 72 patients were unable to identify the odor of coffee, and 35 per cent could not identify the odor of cinnamon. Parkinsonian patients who were normal on a picture identification test (PIT) similar to the UPSIT in format were tested for their detection and recognition of odors (Doty and Snow, 1988). Of these 59 patients, 29 had scores on the UPSIT that were below the 10th percentile for their age and sex, and an additional 16 patients had scores between the 10th and 25th percentiles. These patients also showed marked impairment on a phenyl ethyl alcohol detection threshold task (Doty and Snow, 1988). Deficits in odor identification in these patients were independent of age, which produces a steady decline in performance on the UPSIT beyond age 60 years (Doty et al, 1984b). Parkinson's patients between the ages of 40 and 49 years scored about the same as patients and controls between the ages of 80 and 89 years (Doty and Snow, 1988). Olfactory thresholds have been shown to be unrelated to pharmacologic manipulation of dopaminergic or cholinergic status in parkinsonian patients (Quinn et al, 1987), suggesting little or no role for these neurotransmitters in the olfactory impairment. Finally, it has recently been established that Alzheimer's disease is associated with olfactory deficits in both odor identification and threshold (Doty et al, 1987; Serby, 1986). Relative to age, gender-, and race-matched controls, patients with well-defined Alzheimer's disease were deficient on the UPSIT and in phenyl ethyl alcohol threshold tests (Doty et al, 1987). Scores on these tests for the Alzheimer's patients and their matched controls are shown. Although there was overlap in the range of scores on the UPSIT, only

two of the patients evidenced UPSIT scores greater than those of their respected matched controls. Differences between patients and controls were highly significant for both odor identification and detection (Doty et al, 1987). All of thee patients scored in the normal range on the PIT, which demonstrates that they had the cognitive ability to take the UPSIT. Only 2 of the 34 Alzheimer's patients were aware of an olfactory impairment before testing. The olfactory deficits seen in Alzheimer's disease are probably related to the existence of neuritic plaques and neurofibrillary tangles throughout olfactory-related brain structures (Esiri and Wilcock, 1984; Pearson et al, 1985). In fact, several dementia-related disorders, which result in lesions in the olfactory pathways, are accompanied by olfactory deficits, including Huntington's chorea (Moberg et al, 1984), Parkinson's disease (Ansari and Johnson, 1975; Doty and Snow, 1988; Quinn et al, 1987; Ward et al, 1983), and Korsakoff's psychosis (Jones et al, 1975; Mair et al, 1986). It has even been proposed that the olfactory system could be the route of invasion of etiologic factors responsible for some of these diseases (Shipley, 1985).

Several kinds of nutritional deficiencies have been implicated in taste and smell dysfunction. Taste sensitivity has been reported to be diminished, presumably secondary to cachexia, in patients with a variety of cancers (DeWys and Walters, 1975). Women with estrogen receptor-positive breast cancer have been shown recently to have increased olfactory thresholds (Lehrer et al, 1985). These conditions are distinct from the effects of radiation and chemotherapy on the taste sensitivity of cancer patients (Conger, 1973; Kalmus and Farnsworth, 1959) or from the acquired food aversions that sometimes occur following these treatments (Bernstein and Webster, 1980). Disturbances of taste or smell in malnutrition or in other systemic conditions, such as pellagra or pernicious anemia, have been attributed to vitamin or trace metal imbalances (Green, 1971; Henkin and Bradley, 1969; Rundles, 1946). Early work by Henkin and his colleagues (Henkin et al, 1967; Henkin and Bradley, 1969; Schechter et al, 1972) suggested that reduced serum copper levels resulted in depressed taste sensitivity, which could be reversed by copper sulfate or zinc sulfate administration. As a result, it has become relatively standard practice to prescribe zinc sulfate for both taste and smell deficiencies, regardless of their causes (Estrum and Renner, 1987). However, there is little evidence that zinc therapy is an effective treatment for taste and smell dysfunction (Price, 1986). Double-blind clinical trials using a cross-over design, in which zinc sulfate was compared with placebo, showed no significant effects of zinc in the treatment of hypogeusia (Henkin et al, 1976). In cases of zinc deficiency caused by renal disease (Atkin-Thor et al, 1978; Mahajan et al, 1980) and hepatic cirrhosis (Weisman et al, 1979), double-blind studies have shown that decreased taste acuity can be restored by treatment with zinc sulfate. Thus, when zinc-deficient states are accompanied by hypogeusia, correction of the zinc deficiency often restores taste sensitivity, but there is no reason to assume that any particular case of taste or smell dysfunction is the result of zinc deficiency or that it would be helped by zinc sulfate therapy (Price, 1986).

Many of the remaining disorders listed in Tables 1 and 2 represent factors already discussed as common causes of taste or smell dysfunction, such as allergic rhinitis, influenzalike infections, sinusitis, periodontitis, and exposure to toxic chemicals. A few additional disorders, such as various intranasal or intracranial tumors, are well known as potential causes of olfactory loss or distortion (Doty, 1979; Feldman et al, 1986; Kimmelman, 1986; Leopold, 1986a), although their occurrence in patients presenting only with olfactory symptoms is relatively rare (Goodspeed et al, 1986a, 1987). Similarly, although taste and

olfactory symptoms may be manifested in psychiatric disturbances (Amsterdam et al, 1987; Kerekovic, 1972; Pryse-Phillips, 1971), these are not typically the kind of patients presenting with taste or smell complaints. However, it is clear that disturbances of taste and smell may result from a wide variety of underlying causes (Tables 1 and 2), making the diagnosis and treatment of these disorders a difficult and challenging problem. As more specific information becomes available from the various taste and smell research centers, these patients should become easier to manage.

Table 1. Disorders Associated With Olfactory Dysfunction

Disorder	Reference
Endocrine	
Adrenocortical insufficiency	Henkin (1975)
Cushing's syndrome	Kallmann et al (1944)
Cystic fibrosis	Weiffenbach and McCarthy (1984)
Diabetes mellitus	Jorgensen and Buch (1961)
Kallmann's syndrome	Kallmann et al (1944)
Primary amenorrhea	Marshall and Henkin (1971)
Pseudohypoparathyroidism	Henkin (1968)
Turner's syndrome	Henkin (1967c)
Neurologic	
Alzheimer's disease	Doty et al (1987)
Epilepsy	Eskenazi et al (1986)
Familial dysautonomia	Henkin and Kopin (1964)
Head trauma	Sumner (1964)
Huntington's chorea	Moberg et al (1984)
Multiple sclerosis	Wender and Szemza (1971)
Parkinson's disease	Ansari and Johnson (1975)
Temporal lobectomy	Eskenazi et al (1983)
Nutritional	
Chronic renal failure	Schiffman et al (1978)
Cirrhosis of the liver	Burch et al (1978)
Cyanocobalamin (B_{12}) deficiency	Rundles (1946)
Korsakoff's psychosis	Jones et al (1975)
Local diseases - mechanical obstruction	
Adenoid hypertrophy	Ghorbanian et al (1983)
Allergic rhinitis	Fein et al (1966)
Atrophic rhinitis (ozena)	Strandbygard (1954)
Bronchial asthma	Fein et al (1966)
Deformity secondary to trauma	Doty and Kimmelman (1986)
Exposure to toxic chemicals	Amoore (1986)
Laryngectomy	Mozell et al (1986)
Leprosy	Barton (1974)
Malignancy of paranasal sinuses with extension	Doty and Kimmelman (1986)
Nasal polyposis	Fein et al (1966)
Nasal surgery	Champion (1966)
Sinusitis	Ryan and Ryan (1974)
Sjögren's syndrome	Henkin et al (1972)
Tumors of nasopharynx with extension	Doty and Kimmelman (1986)
Vasomotor rhinitis	Griffith (1976)

Psychiatric	
Depression	Pryse-Phillips (1971)
Olfactory reference syndrome	Pryse-Phillips (1971)
Schizophrenia	Kerekovic (1972)
Intracranial tumors	
Aneurysms of the anterior communicating bifurcation	Jefferson (1961)
Frontal lobe glioma	Elsberg (1935)
Olfactory groove meningioma	Bakay and Cares (1972)
Suprasellar meningioma	Elsberg (1935)
Temporal lobe tumors	Furstenberg et al (1943)
Intranasal tumors	
Adenocarcinoma	Skolnik et al (1966)
Inverted papilloma	Skolnik et al (1966)
Melanoma	Skolnik et al (1966)
Neuroblastoma	Joachims et al (1975)
Squamous cell carcinoma	Skolnik et al (1966)
Viral and infectious conditions	
Acute viral hepatitis	Henkin and Smith (1971)
Herpes simplex	Toomey et al (1979)
Influenzalike infections	Henkin et al (1975).

Table 2. Disorders Associated With Gustatory Dysfunction

Disorder	Reference
Endocrine	
Adrenocortical insufficiency	Henkin (1975)
Congenital adrenal hyperplasia	Henkin (1975)
Cretinism	Shepard and Gartler (1960)
Cushing's syndrome	Henkin (1975)
Diabetes mellitus	Settle (1986)
Hypothyroidism	McConnel et al (1975)
Panhypopituitarism	Henkin (1975)
Pseudohypoparathyroidism	Henkin (1968)
Turner's syndrome	Henkin (1967c)
Neurologic	
Bell's palsy	Ekstrand (1979)
Familial dysautonomia	Henkin and Kopin (1964)
Head trauma	Schecter and Henkin (1974)
Multiple sclerosis	Catalanotto et al (1986)
Pontine hemorrhage	Goto et al (1983)
Raeder's paratrigeminal syndrome	Fisher (1971)
Nutritional	
Cachexia	DeWys and Walters (1975)
Chronic renal failure	Ciechanover et al (1980)
Cirrhosis of the liver	Burch et al (1978)
Niacin (vitamin B_3) deficiency	Green (1971)
Local alterations of taste buds	
Chemicals, drugs	Rollin (1966)
Radiation therapy	Conger (1973)
Sjögren's syndrome	Henkin et al (1972)
Psychiatric	
Depression	Amsterdam et al (1987)
Schizophrenia	Doty and Kimmelman (1986)
Tumors and surgery	
Base of skull neoplasia	Doty and Kimmelman (1986)
Laryngectomy	Kashima and Kalinowski (1979)
Oral cavity cancer	Doty and Kimmelman (1986)
Viral and infectious	
Gingivitis	Goodspeed et al (1986a)
Glossitis	Brenner and Simon (1984)
Influenzalike infections	Henkin et al (1975)
Periodontitis	Goodspeed et al (1987).