TASTE AND SMELL PERCEPTION IN THE ELDERLY: EFFECT OF MEDICATIONS AND DISEASE

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I. INTRODUCTION

During the 21st century, there will be substantial shifts in the demographics of the world's population with increases in both the number and percentage of elderly persons (United States Bureau of the Census, 1996; Wattenberg, 1976; American Association of Retired Persons, 1995). There are currently over 400 million people in the world aged 65 and greater (Davies, 1989); by the year 2025, the elderly population is expected to reach 1.121 billion people (US Senate Special Committee on Aging, 1985–1986). In order to provide food and nutrition that meet the needs of older individuals, the special sensory and nutritional requirements of this population must be taken into account.

This paper describes the changes in the senses of taste and smell that occur with advancing age. The incidence of taste and smell disorders will increase significantly over the coming decades due to the rapid growth in the elderly segment of the population. Furthermore, elderly individuals will likely experience taste and smell losses for a greater proportion of their lives due to the increase in life expectancy. Taste and smell disorders in the elderly present a public health challenge because they can increase the risk of malnutrition and food poisoning. Furthermore, taste and smell impairments reduce the quality of life (Schiffman, 1997).

Taste and smell are termed chemical senses because they respond to molecules in foods, liquids, and air. The chemical senses play a fundamental role in food intake, digestion, and satiation. First, they are involved in the generation of digestive secretions necessary for the absorption of nutrients. Taste and smell signals trigger salivary, gastric, pancreatic, and intestinal secretions which are termed cephalic phase responses (Giduck *et al.*, 1987). Second, chemosensory signals serve as indicators of a food's nutritional value from learned association of a food's taste/smell with its post-ingestive effects (Booth, 1985; Schiffman and Warwick, 1992). This learned association enables the consumer to detect and discriminate among foods in the face of fluctuating nutritional requirements and to modulate food intake and meal size in anticipation of its nutritional consequences. Avoidance of toxins is also achieved by learned associations between taste/smell sensations and the physiological consequences of ingestion. Third, taste and smell sensations provide information about palatability of food prior to ingestion; furthermore they are primary reinforcers of eating and induce feelings of satiety (Schiffman and Warwick, 1992; Scott, 1992).

Deficits in taste or smell perception are a consequence of normal aging, certain disease states (especially Alzheimer's disease), medications, surgical interventions, and/or environmental exposure (Schiffman, 1983,

1997; Schiffman and Nagle, 1992). Impaired taste and smell perception in the elderly can lead to poor appetite (de Jong *et al.*, 1999), inappropriate food choices (Duffy *et al.*, 1995), lower nutrient intake (Griep *et al.*, 1996; Schiffman, 1997), and impaired nutritional status and immunity (Schiffman, 1983, 1997; Schiffman and Wedral, 1996). Poor appetite is one cause of decreased energy consumption in the elderly (Morley, 1997; Morley and Thomas, 1999; Chapman and Nelson, 1994). Reduced energy consumption impacts protein and micronutrient status which, in turn, may induce subclinical deficiencies that directly affect function (Morley, 1997; Chapman and Nelson, 1994; Blumberg, 1997). Loss of taste, smell, and appetite are especially serious in elderly patients who are critically ill and thus at high risk for protein-energy malnutrition as well as micronutrient deficiencies (Opper and Burakoff, 1994; Schiffman and Wedral, 1996). For elderly who live in developing nations where there is chronic poverty, taste and smell losses may further exacerbate malnutrition.

An overview of the current literature on taste and smell perception indicates that a significant proportion of elderly individuals experience chemosensory losses during their lifetimes (Schiffman, 1997; Doty *et al.*, 1984). Both longitudinal and cross-sectional data suggest that chemosensory losses become noticeable after the age of 60 years (although they may occur earlier) with increasing severity of loss after the age of 70 (Doty *et al.*, 1984; Schiffman and Warwick, 1991). The taste system is more robust than the smell system until medication use increases (Schiffman, 1997). The medical terms used to classify impairments of taste and smell include: ageusia (no taste sensation), hypogeusia (decreased taste sensation), dysgeusia (distorted taste sensation), anosmia (no sensation of smell), hyposmia (decreased sensation of smell), and dysosmia (distorted smell sensation) (Schiffman, 1983). Distortions in taste and smell (i.e. dysgeusia and dysosmia) can occur in the presence or absence of a chemical stimulus and are not necessarily associated with loss of sensitivity (Cowart *et al.*, 1989). For example, patients with dysgeusia often complain about bitter or metallic side tastes that are not characteristic of the foods they are eating. They may also experience an unpleasant taste in their mouths in the absence of food. While dysgeusia and dysosmia are difficult to quantify in psychophysical experiments, ageusia, hypogeusia, anosmia, and hyposmia can be quantified by measuring responses to taste and/or smell stimuli at both threshold and suprathreshold concentrations.

It should be noted here that many elderly are not consciously aware of their taste and smell impairments. Unlike sensory losses of vision or audition which elderly corrrectly attribute to changes in their own bodies, altered taste and smell are frequently attributed to outside sources. For

example, elderly will state that "Food doesn't taste as good as it did in the old country" (i.e. they believe that food quality was better when they were young). Elderly in retirement communities routinely complain about the food even when it is of high quality. The underlying cause of these complaints, however, in reality is physiological impairment of the taste and smell systems which reduces the pleasure derived from food and beverages (Lucas and Schiffman, 1999). The attribution of chemosensory deficits to problems outside themselves (such as inferior quality of food) accounts in part for the finding of Nordin *et al.* (1995) that approximately 75% of normal elderly with smell loss reported "normal" smell sensitivity.

This chapter will provide a review of our current state of knowledge about: (1) age-related changes in the physiology and anatomy of the taste and smell systems, (2) perceptual changes in taste and smell with age, and (3) effect of diseases and medications on taste and smell perception. Methods for compensating for taste and smell losses with flavor-enhanced foods will also be described that can improve appetite, food palatability and/or intake, increase salivary flow and immunity, and reduce oral complaints in both sick and healthy elderly (Schiffman, 1979, 1997, 1998; Schiffman and Warwick, 1993; Schiffman and Miletic, 1999; Schiffman and Graham, 2000).

II. PHYSIOLOGY OF TASTE AND SMELL AND THEIR ALTERATIONS WITH AGE

To understand the nature of taste and smell losses in the elderly, it is necessary to consider the physiology and anatomy of these chemosensory pathways.

A. TASTE

The peripheral receptor cells for taste are polarized neuroepithelial cells clustered into buds and distributed on the dorsal surface of the tongue, tongue–cheek margin, base of the tongue near ducts of the sublingual glands, the soft palate, pharynx, larynx, epiglottis, uvula, and first one-third of the esophagus (Norgren, 1990; Reutter and Witt, 1993; Scott, 1992). Taste sensations are produced by the interaction of chemicals (e.g. from food) with taste buds during ingestion, chewing, and swallowing. Taste buds consist of approximately 50–100 cells arranged in an onion-like structure. The taste cells extend from the base of the bud to the taste pit where they terminate as microvillar taste hairs that project into the mucus of the pit. The apical margin of the pit extends to the epithelial

surface to form the taste pore, which averages 4–10 microns in diameter. Approximately 10–20 cells in a bud make contact with the tastants in the pit. Taste sensations are transduced when chemicals interact with receptors or channels in the cell surface membranes of the taste cells. Anatomical studies have shown that individual cells in taste buds differ structurally but it is not known currently whether cells that differ in appearance have different taste functions. Cells similar to taste receptor-like cells are also found in the mucosa of the stomach and intestine (Höfer *et al.*, 1996).

The individual taste cells in a bud undergo continuous renewal every 10–10.5 days. The continuous turnover of cells in the renewing taste epithelium involves two death factors Bax (a death factor in the Bcl-2 family of survival/death factors) and p53 (a tumor-suppressor protein linked to apoptosis and Bax transcription). Old taste receptor cells employ p53 and Bax as part of their apoptotic death pathway (Zeng and Oakley, 1999). This process of continuous renewal can be impaired by protein malnutrition that affects the reproduction of taste cells and reduces taste sensitivity (Schiffman, 1983).

Taste buds on the tongue are situated on specialized epithelial projections termed papillae. There are three different kinds of lingual papillae that contain taste buds: fungiform papillae (which are shaped somewhat like mushrooms), foliate papillae (which consist of linear depressions or vertical folds), and circumvallate papillae (which are surrounded by deep moats). There are approximately 200 fungiform papillae located on the anterior two-thirds of the tongue, with the highest concentration at the tip of the tongue. Fungiform papillae bear 1–20 taste buds at their apex. Foliate papillae are situated on the posterior-lateral sides of the tongue and tend to be especially sensitive to sour tastes. Circumvallate papillae are found on the posterior tongue arranged in a chevron-shaped form pointing caudally; circumvallate papillae contain the largest number of taste buds. There are 8–12 circumvallate papillae in humans with the taste buds located in deep moats surrounding the papillae. The burrows and trenches of both foliate and circumvallate papillae contain seromucous secretions that derive from von Ebner's glands and are believed to circulate tastants so that they come in contact with receptors. In addition, these seromucous secretions remove waste from the crypts of the foliate and circumvallate papillae. A fourth type of papilla also occurs on the tongue (filiform papillae) but it does not contain taste buds. Filiform papillae are conical projections of epithelium on the tongue which function to provide friction for movement of food. The entire tongue is sensitive to all taste qualities but there are regional differences in sensitivity, i.e. fungiform papillae are more sensitive to sodium salts, foliate papillae to acids, and circumvallate to bitter compounds.

There appear to be few anatomical losses in the numbers of papillae and/or taste buds in older individuals (Bradley, 1988; Mistretta, 1984; Arvidson and Friberg, 1980). However, functional loss in various regions of the tongue does occur in the elderly (Matsuda and Doty, 1995; Bartoshuk *et al.*, 1987) which suggests that sensory loss does occur even if there is not a physical diminution in the number of taste buds or papillae. Current opinion is that taste losses in normal aging in the presence or absence of disease may be due, in part, to changes at the level of the taste cell membranes (e.g. altered functioning of ion channels and receptors) rather than losses in the number of taste buds (see Mistretta, 1984).

A variety of ion channels and cell-surface receptors along with second messenger systems are responsible for differences in taste quality (Kinnamon and Margolskee, 1996; Spielman *et al.*, 1992). The salty taste of sodium salts results when Na^+ ions traverse sodium channels in the membranes of taste cells (Schiffman *et al.*, 1983). The taste of potassium salts, like sodium salts, involves conductance of the potassium cation through taste cell membranes (Kim and Mistretta, 1993). Some but not all sweet compounds bind to seven-membrane-spanning cell surface receptors that activate the adenylate cyclase second messenger cascade (Lindemann, 1996). At least two pathways play a role in bitter taste transduction: (1) the phosphatidylinositol second messenger cascade, and (2) the alpha-gustducin/phosphodiesterase pathway (Lindemann, 1996). Little is known about changes in these biochemical pathways with aging.

Taste bud cells form direct neural connections called synapses with three nerves: the facial (cranial nerve VII), glossopharyngeal (cranial nerve IX), and vagus (cranial nerve X). These three cranial nerves relay signals from taste receptor cells to the rostral portion of the nucleus of the solitary tract (NST) in the medulla in the brain stem (Pritchard, 1991; Scott, 1992). Taste buds on the anterior two-thirds of the tongue as well as the anterior walls of the foliate papillae are innervated by the chorda tympani nerve (one branch of cranial nerve VII). The chorda tympani nerve passes through the middle ear where it can be damaged by micro-organisms as in otitis media or during surgery as for acoustic neuroma. The greater superficial petrosal nerve (another branch of cranial nerve VII) relays information from most taste buds of the soft palate although a few are innervated by the deep petrosal branch of the glossopharyngeal nerve. Loss of sensory perception on the soft palate occurs in persons with dentures that cover this mouth region. Taste buds in the circumvallate papillae and those in the posterior walls of the foliate papillae are innervated by the glossopharyngeal nerve. There are interactions between the chorda tympani nerve and glossopharyngeal nerve. Stimulation of the chorda tympani nerve normally inhibits responses from the glossopharyngeal

nerve; anesthetizing the chorda tympani nerve leads to potentiation of bitter taste responses from the circumvallate papillae contralateral to the anesthetized side (Lehman *et al.*, 1995; Yanagisawa *et al.*, 1998; Catalanotto *et al.*, 1993). The superior laryngeal branch of the vagus nerve innervates taste buds located on the far posterior tongue, the epiglottis, the larynx, and the esophagus.

The NST not only receives information from the gustatory system but also from the olfactory (first cranial) nerve (Van Buskirk and Erickson, 1977) and from visceral sensory fibers that originate in the esophagus, stomach, intestines, and liver (Pritchard, 1991; Schiffman and Warwick, 1992). These visceral projections terminate in the caudal portion of NST. This intermingling of taste, smell, and visceral inputs in NST is responsible in part for the impact of the chemical senses on metabolic activity and digestive secretions. The converse also occurs, e.g. the activity in taste neurons can be modified by transient physiological status (Contreras and Frank, 1979; Jacobs *et al.*, 1988; Giza *et al.*, 1993). Axons from the taste portion of NST project to the ventroposteromedial nucleus of the thalamus and ultimately to the cortex. Axons from the visceral division of NST branch to the parabrachial nucleus with subsequent projections to lateral hypothalamus, amygdala, and the bed nucleus of stria terminalis. Little is known about age-related losses in the neural taste pathways to NST or higher neural centers that mediate taste.

Pungent qualities in the oral cavity (e.g. from chili peppers, ginger, or carbonation) as well as temperature and touch are transmitted by cranial nerve V (the trigeminal nerve) as well as free nerve endings of cranial nerves VII, IX, and X (Green, 1996). Trigeminal nerve fibers terminate in fungiform and foliate papillae on the anterior two-thirds of the tongue. The trigeminal nerve also transmits information about the texture of food such as oily sensations. Sensory information transmitted by the trigeminal nerve is not considered a "taste" because the trigeminal nerve is not directly stimulated by electrical signals from taste buds; rather trigeminal stimulation involves a different sense called chemesthesis which is related to nociception (Green, 1996). However, recent data on a phenomenon called "thermal taste" suggests that there is some interaction between chemesthesis and taste. Warming the anterior edge of the tongue from a cold temperature can evoke sweetness, whereas cooling can evoke sourness and/or saltiness (Cruz and Green, 2000). More data are necessary to understand the mechanism(s) for this phenomenon.

B. SMELL

Odor sensations occur when odorants interact with olfactory receptor neurons that are situated in the olfactory mucosa located on the dorsal

aspect (top) of the nasal cavity, the septum, and part of the superior turbinate bones in the nose (Schiffman, 1997). There are three types of cells in the olfactory mucosa: (1) olfactory neurons which are bipolar cells with cilia projecting from their terminal ends to form a characteristic dense ciliary blanket where volatile compounds first contact the olfactory receptors in the olfactory epithelium, (2) supporting or sustentacular cells that terminate in microvilli that move mucus around, and (3) basal cells (like stem cells) which make new olfactory receptor cells. The number of olfactory receptor cells is vast, approximately 10^6 in man and 10^8 in rabbits (Moulton, 1974). In rats and dogs the olfactory epithelium is easily distinguishable due to its yellowish color; in humans it is more difficult to visualize because it is pinkish and blends with the respiratory epithelium which lines the rest of the nasal cavity. Odorants (the chemicals that induce odor) reach the olfactory receptors via orthonasal transport through the nares or via retronasal transport from the oral cavity. In orthonasal transport, the structure of the nose with its bony turbinates creates turbulent airflow patterns that direct volatile compounds to the olfactory receptor cells in the top of the nasal cavity.

Current biochemical studies suggest olfactory transduction commences with the binding of an odorant ligand to a protein receptor on the olfactory neuron cell surface. This initiates a cascade of enzymatic reactions that include the production of a second messenger and the eventual depolarization of the cell membrane. Olfactory receptors have seven transmembrane regions and belong to a G-protein-coupled receptor superfamily that transmits information via adenylate cyclase and phosphoinositol signaling cascades (Breer, 1994; Buck and Axel, 1991). As many as 1000 different types of odorant receptors are thought to exist (approximately 1% of the human genome), but individual olfactory sensory neurons express only one odorant receptor type (Mombaerts, 1999). Yet, single olfactory cells respond to a range of compounds with a variety of olfactory qualities. The location of odorant binding is thought to be a hydrophobic pocket in transmembrane regions 3, 4, and 5 of the seven-membrane-spanning receptor. Expression of a particular olfactory receptor has been achieved in vivo in the rat by using an adenovirus vector as a tool for gene transfer to infect the nasal epithelia (Zhao *et al.*, 1998). Olfactory neurons, like taste cells, are continuously shed but the average time for replacement is three times longer, i.e. approximately 30 days. This regeneration of neurons is unique since other neurons in the adult central nervous system are generally not replaced.

Axons of the olfactory bipolar cells course through tiny holes in the cribriform plate of the ethmoid bone to the olfactory bulb where they make their first synapses with second-order neurons in intricate neural

masses called glomeruli. Damage to olfactory neurons (and hence smell perception) can result when the neurons passing through the cribriform plate are severed (e.g. in falls that frequently occur in the elderly). Axons from first order olfactory neurons form stereotypical projection patterns onto specific glomeruli at fixed locations. The glomeruli of the olfactory bulb (about 2000 in number) represent the first tier of central information processing for odors (Mori and Yoshihara, 1995). Axons for all sensory neurons expressing a single odorant receptor type are thought to converge onto two or three glomeruli in the olfactory bulb. Individual olfactory sensory neurons can respond to multiple odorants so it is the pattern across multiple glomeruli that codes olfactory quality. Glomeruli in the elderly tend to atrophy as fibers degenerate and disappear taking on an appearance of Swiss cheese.

The olfactory tract courses caudally through the medial aspects of the olfactory bulb projecting to the anterior olfactory nucleus, the olfactory tubercle, the prepyriform cortex, and the amygdala and ultimately to higher brain centers that process the olfactory signals. The prepyriform cortex and the amygdala are brain structures that are part of the so-called limbic system, which processes emotions and memories as well as olfactory signals. Olfactory information is ultimately transmitted to the hypothalamus (which mediates food intake) and then to the neocortex. Noninvasive techniques are currently being used to study cortical responses to different chemical stimuli in humans; these studies suggest that the pyriform cortex, orbitofrontal areas, and parts of the parietal and temporal cortices are activated by odorants with varying odor qualities (Kettenmann *et al.*, 1996; Zald and Pardo, 1997). However, there are significant differences in the degree of activation of these areas dependent on the odor quality and pleasantness of the stimulus.

A range of anatomic and physiologic modifications of the olfactory epithelium, olfactory bulb and nerves, hippocampus and amygdaloid complex, and hypothalamus occur with age, and these changes parallel perceptual losses in the olfactory system during the aging process. These include: reduced protein synthesis and structural alterations in olfactory epithelium (Dodson and Bannister, 1980; Naessen, 1971), atrophy in olfactory bulb and nerve (Hinds and McNelly, 1981; Liss and Gomez, 1958; Smith, 1942), presence of senile plaques and neurofibrillary tangles in hippocampus and amygdaloid complex (Scheibel and Scheibel, 1975; Tomlinson and Henderson, 1976), hypothalamic degeneration including disruption of hypothalamic architecture paralleled by deterioration and loss of dendritic surface (Machado-Salas *et al.*, 1977), altered calcium homeostasis in the hippocampus leading to elevated intracellular calcium (Landfield and Pitler, 1984), and hippocampal pathology including an

increase in reactive astrocytes associated with elevated plasma adrenocorticoids (Landfield *et al.*, 1978). Degeneration involves damage to cells, reduced cell numbers, and diminished levels of neurotransmitters (Schiffman, 1983; Leopold *et al.*, 1989; Morrison and Costanzo, 1992). Recent data suggest that loss in olfactory function may also lead to a concomitant decrease in trigeminal sensitivity (Hummel *et al.*, 1996) but the mechanism for this observation is not known.

III. PERCEPTION OF TASTE AND SMELL IN THE ELDERLY

Most studies of chemosensory perception in the elderly support age-related losses at both the threshold level as well as suprathreshold levels (Schiffman, 1997; Doty *et al.*, 1984; Wysocki and Gilbert, 1989; Stevens and Dadarwala, 1993). Suprathreshold impairments include reduced perceived intensity of stimuli, diminished ability to discriminate among chemosensory stimuli, and deficits in the ability to identify odors and taste on the basis of taste and smell.

A. TASTE

Current textbooks on sensory perception usually state that there are only four "basic" tastes (sweet, sour, salty, and bitter). There is emerging experimental evidence, however, in a variety of species including rodents, monkeys, and humans that the full range of taste quality is far broader than four so-called "basic" tastes (reviewed in Schiffman, 2000). Chemicals with qualities such as metallic (iron salts), umami (monosodium glutamate/5′-nucleotides), chalky (calcium salts), and even fatty appear to activate taste neurons (Schiffman and Erickson, 1993; Plata-Salaman *et al.*, 1992; Schiffman, 2000; Gilbertson *et al.*, 1997). Most studies have reported losses for all of these taste qualities in the elderly. Generally, the sense of taste is not totally absent (ageusia) in the elderly, but rather it is reduced (hypogeusia, i.e. elevated thresholds or loss in suprathreshold sensitivity) or is distorted (dysgeusia).

1. Losses of taste at threshold concentrations

Taste detection thresholds as well as recognition thresholds are elevated in older individuals (Schiffman, 1993; Stevens *et al.*, 1995; Murphy, 1993), but the degree of loss depends on the chemical structure of the compounds tested as well as the disease states, medications, surgical interventions, and environmental exposures that an individual has experienced

(Schiffman, 1983, 1993). A taste detection threshold is the lowest concentration at which a tastant is correctly distinguished from a diluent such as water; a taste recognition threshold is the lowest concentration at which a tastant is correctly identified. Age-related losses for so-called "basic" tastes such as NaCl (salty), sucrose (sweet), citric acid (sour), and quinine HCl (bitter) using whole mouth stimulation are minimal in elderly who suffer from no diseases and take no prescription medications (see Table I). The only taste losses that reached statistical significance in these very healthy elderly were for NaCl. However, far greater losses occur in those elderly taking medications but who otherwise live active, normal lives. The average detection thresholds for elderly individuals with one or more medical conditions and taking an average of 3.4 medications were significantly elevated compared to a young cohort, i.e. 11.6 times higher for sodium salts (see Table II); 2.7 times higher for sweeteners (see Table III); 4.3 times higher for acids (see Table IV); 7.0 times higher for bitter compounds (see Table V); 2.5 times higher for amino acids (see Table VI); 5.0 times higher for glutamate salts (see Table VII). This is an average loss across these taste qualities of 5.41. Age-related losses in the oral and taste perception of oil-in-water emulsions are given in Table VIII; detection thresholds for oil-in-water emulsions in the elderly were on average 3.14 times higher than for young subjects. Hospitalized elderly patients suffering from involuntary weight loss have even more severe taste losses at the threshold level (Schiffman and Wedral, 1996).

Thresholds for oral trigeminal stimulants such as capsaicin (8-methyl-N-vanillyl-6-noneamide), however, showed a different pattern with age (Schiffman and Graham, 1991). Capsaicin, a component in red chili pepper,

TABLE I

MEAN DETECTION THRESHOLDS FOR TASTE OVER THE LIFESPAN FOR PERSONS TAKING NO PRESCRIPTION MEDICATIONS AND HAVING NO MEDICAL PROBLEMS

Age in years	NaCl[1]	Sucrose	Citric acid	Quinine HCl
70–79	0.036 M[a]	0.045 M	0.0014 M	0.161 mM
60–69	0.031 M[a,b]	0.030 M	0.0012 M	0.0012 mM
50–59	0.028 M[a,b]	0.028 M	0.0015 M	0.0132 mM
40–49	0.018 M[a,b]	0.038 M	0.0014 M	0.0615 mM
30–39	0.016 M[b]	0.033 M	0.0003 M	0.0915 mM
20–29	0.013 M[b]	0.025 M	0.0008 M	0.0535 mM
10–19	0.023 M[a,b]	0.024 M	0.0011 M	0.0601 mM

[1] Means with the same letters are statistically equivalent

Source: Data from Schiffman, 1994

TABLE II
MEAN DETECTION THRESHOLDS FOR SODIUM SALTS AT pH 7.0

Stimulus	Young (Y)	Elderly (E)	E/Y (ratio of elderly to young)
Monosodium glutamate	0.00126 M	0.00638 M	5.06
Na acetate	0.00242 M	0.0190 M	7.84
Na ascorbate	0.00404 M	0.0250 M	6.19
Na carbonate	0.00218 M	0.00829 M	3.79
Na chloride	0.00238 M	0.01850 M	7.76
Na citrate	0.000531 M	0.0130 M	24.5
Na phosphate monobasic	0.00307 M	0.0160 M	5.21
Na succinate	0.000854 M	0.0138 M	16.2
Na sulfate	0.000981 M	0.0283 M	28.8
Na tartrate	0.00151M	0.0159M	10.5

Source: Data from Schiffman *et al.*, 1990b

TABLE III
MEAN DETECTION THRESHOLDS FOR SWEETENERS

Stimulus	Young (Y)	Elderly (E)	E/Y (ratio of elderly to young)
Acesulfam-K	4.44×10^{-5} M	7.47×10^{-5} M	1.68
Aspartame	2.24×10^{-5} M	9.13×10^{-5} M	4.07
Calcium cyclamate	2.66×10^{-4} M	4.12×10^{-4} M	1.55
Fructose	4.39×10^{-3} M	10.1×10^{-3} M	2.30
Monellin	1.95×10^{-8} M	9.13×10^{-8} M	4.67
Neohesperidin dihydrochalcone	2.20×10^{-6} M	4.60×10^{-6} M	2.09
Rebaudioside	4.61×10^{-6} M	13.0×10^{-6} M	2.82
Sodium saccharin	1.47×10^{-5} M	4.24×10^{-5} M	2.88
Stevioside	5.31×10^{-6} M	16.0×10^{-6} M	3.02
Thaumatin	7.16×10^{-8} M	13.3×10^{-8} M	1.86
D-tryptophan	1.09×10^{-4} M	3.22×10^{-4} M	2.95

Source: Data from Schiffman *et al.*, 1981

conveys a burning sensation in the mouth. Capsaicin was dissolved in ethanol, impregnated in small rectangles of chromatography paper, and dried to evaporate the ethanol solvent. The mean detection threshold for capsaicin delivered by chromatography paper was found to be 1.00 ppm ± 1.07 for 20 young subjects (18 to 25 years of age) and 4.83 ppm ± 3.52 for 20 middle-aged subjects (45 to 60 years of age). None of the young or middle-aged subjects were taking medications other than estrogen. The

TABLE IV
MEAN DETECTION THRESHOLDS FOR ACIDS

Stimulus	Young (Y)	Elderly (E)	E/Y (ratio of elderly to young)
Acetic	0.000106 M	0.000273 M	2.58
Ascorbic	0.000281 M	0.000725 M	2.58
Citric	0.0000498 M	0.000375 M	7.53
Glutamic	0.0000920 M	0.000463 M	5.03
Hydrochloric	0.0000179 M	0.0002 M	11.17
Succinic	0.000132 M	0.000188 M	1.42
Sulfuric	0.0000468 M	0.000100 M	2.14
Tartaric	0.0000864 M	0.000163 M	1.89

Source: Data from Schiffman, 1993

TABLE V
MEAN DETECTION THRESHOLDS FOR BITTER TASTES

Stimulus	Young (Y)	Elderly (E)	E/Y (ratio of elderly to young)
Caffeine	1.30×10^{-3} M	1.99×10^{-3} M	1.53
Denatonium benzoate	1.15×10^{-8} M	3.23×10^{-8} M	2.81
KNO_3	1.91×10^{-3} M	3.27×10^{-2} M	17.1
$MgCl_2$	1.02×10^{-3} M	5.20×10^{-3} M	5.10
$MgNO_3$	1.40×10^{-3} M	3.33×10^{-2} M	23.8
$MgSO_4$	3.23×10^{-4} M	6.08×10^{-3} M	18.8
Naringin	4.27×10^{-5} M	1.38×10^{-4} M	3.23
Phenylthiocarbamide	5.91×10^{-4} M	1.26×10^{-3} M	2.13
Quinine HCl	3.99×10^{-6} M	8.07×10^{-6} M	2.02
Quinine sulfate	2.04×10^{-6} M	8.75×10^{-6} M	4.29
Sucrose octaacetate	3.89×10^{-6} M	5.32×10^{-6} M	1.37
Urea	1.03×10^{-1} M	1.16×10^{-1} M	1.12

Source: Data from Schiffman *et al.*, 1994a

mean detection threshold for 20 community-dwelling elderly subjects (70 to 82 years of age) taking an average of 3.2 medications was 3.34 ± 2.62. Interestingly, 20 hospitalized elderly patients taking an average of 6.2 medications had a mean detection threshold of 0.95 ppm ± 2.07 which was similar to young subjects; however, the same hospitalized subjects had very elevated thresholds for NaCl and sucrose. Statistical analysis of these data indicated that aging in the absence of medications tends to increase the threshold for capsaicin while medications and illness

TABLE VI
MEAN DETECTION THRESHOLDS FOR AMINO ACIDS

Stimulus	Young (Y)	Elderly (E)	E/Y (ratio of elderly to young)
L-alanine	1.62×10^{-2} M	1.95×10^{-2} M	1.20
L-arginine	1.20×10^{-3} M	1.12×10^{-3} M	0.93
L-arginine HCl	1.23×10^{-3} M	2.39×10^{-3} M	1.94
L-asparagine	1.62×10^{-3} M	9.33×10^{-3} M	5.75
L-aspartic acid	1.82×10^{-4} M	5.01×10^{-4} M	2.75
L-cysteine	6.30×10^{-5} M	3.90×10^{-4} M	6.19
L-cysteine HCl	1.60×10^{-5} M	2.00×10^{-5} M	1.25
L-glutamic acid	6.30×10^{-5} M	1.00×10^{-4} M	1.59
L-glutamine	9.77×10^{-3} M	2.69×10^{-2} M	2.75
L-glycine	3.09×10^{-2} M	6.17×10^{-2} M	2.00
L-histidine	1.23×10^{-3} M	6.45×10^{-3} M	5.24
L-histidine HCl	7.94×10^{-5} M	3.89×10^{-4} M	4.90
L-isoleucine	7.41×10^{-3} M	1.20×10^{-2} M	1.62
L-leucine	6.45×10^{-3} M	1.29×10^{-2} M	2.00
L-lysine	7.08×10^{-4} M	2.24×10^{-3} M	3.16
L-lysine HCl	4.47×10^{-4} M	2.09×10^{-3} M	4.68
L-methionine	3.72×10^{-3} M	2.63×10^{-3} M	0.71
L-phenylalanine	6.61×10^{-3} M	1.91×10^{-2} M	2.89
L-proline	1.51×10^{-2} M	3.72×10^{-2} M	2.46
L-serine	2.09×10^{-2} M	2.63×10^{-2} M	1.26
L-threonine	2.57×10^{-2} M	2.00×10^{-2} M	0.78
L-tryptophan	2.29×10^{-3} M	2.88×10^{-3} M	1.26
L-valine	4.16×10^{-3} M	1.15×10^{-2} M	2.76

Source: Data from Schiffman *et al.*, 1979

counteract the aging effect and lower the threshold. The low thresholds for capsaicin found in sick elderly may be due to sores in the mouth or to leaky membranes subsequent to medication use that increase the interaction of capsaicin with the trigeminal nerve endings. The relative increase in sensitivity to burning/irritation and the decrease in sensitivity to actual tastes such as salty and sweet in sick elderly will increase the salience of the burning or irritant properties of a spicy meal.

2. *Losses of taste at suprathreshold concentrations*

Suprathreshold taste studies for the most part have found that the elderly perceive a broad range of tastes to be less intense than younger persons (Schiffman, 1993; Murphy, 1993; Schiffman and Wedral, 1996). The degree of loss, however, differs across studies, and these differences are probably

TABLE VII

MEAN DETECTION THRESHOLDS FOR GLUTAMATE SALTS (WITH AND WITHOUT INOSINE-5'-MONOPHOSPHATE—IMP)

Stimulus	Young (Y)	Elderly (E)	E/Y (ratio of elderly to young)
Sodium glutamate	9.02×10^{-4} M	2.83×10^{-3} M	3.14
Sodium glutamate with 0.1 mM IMP	1.13×10^{-4} M	8.88×10^{-4} M	7.86
Sodium glutamate with 1 mM IMP	4.80×10^{-5} M	1.45×10^{-4} M	3.02
Potassium glutamate	9.02×10^{-4} M	7.69×10^{-3} M	8.53
Potassium glutamate with 0.1 mM IMP	1.06×10^{-4} M	5.49×10^{-4} M	5.18
Potassium glutamate with 1 mM IMP	1.08×10^{-5} M	9.28×10^{-5} M	8.59
Ammonium glutamate	1.08×10^{-3} M	4.26×10^{-3} M	3.94
Ammonium glutamate with 0.1 mM IMP	1.39×10^{-4} M	4.58×10^{-4} M	3.29
Ammonium glutamate with 1 mM IMP	3.43×10^{-5} M	1.29×10^{-4} M	3.76
Calcium diglutamate	2.92×10^{-4} M	1.09×10^{-3} M	3.73
Calcium diglutamate with 0.1 mM IMP	6.06×10^{-5} M	3.27×10^{-4} M	5.40
Calcium diglutamate with 1 mM IMP	1.90×10^{-5} M	6.92×10^{-5} M	3.64
Magnesium diglutamate	2.53×10^{-4} M	1.86×10^{-3} M	7.35
Magnesium diglutamate with 0.1 mM IMP	4.21×10^{-5} M	2.89×10^{-4} M	6.86
Magnesium diglutamate with 1 mM IMP	2.57×10^{-5} M	4.52×10^{-5} M	1.76
IMP (Inosine 5'-monophosphate)	4.30×10^{-4} M	1.99×10^{-3} M	4.63

Source: Data from Schiffman *et al.*, 1991

due to genetic factors, cognitive status of the subjects, their medical conditions and use of medications, as well as different testing methods. Persons who genetically taste the compound PTC (phenylthiocarbamide)

TABLE VIII

MEAN DETECTION THRESHOLDS FOR THREE OILS IN % (MEDIUM CHAIN TRIGLYCERIDES-MCT, SOYBEAN, AND MINERAL) IN FOUR EMULSIFIERS (ACACIA, EMPLEX, TWEEN-80, AND NA CASEINATE)

Oil	Emulsifier	Young (Y)	Elderly (E)	Ratio E/Y
MCT	Acacia	2.85	10.1	3.54
Soybean	Acacia	4.02	12.9	3.20
Mineral	Acacia	4.43	9.77	2.20
MCT	Emplex	3.93	25.0	6.37
Soybean	Emplex	6.52	14.9	2.28
Mineral	Emplex	8.85	20.0	2.26
MCT	Tween-80	5.35	19.3	3.60
Soybean	Tween-80	5.85	17.7	3.02
Mineral	Tween-80	5.77	19.9	3.49
MCT	Na caseinate	6.18	13.6	2.20
Soybean	Na caseinate	5.35	13.0	2.43
Mineral	Na caseinate	4.27	13.4	3.13

Source: Data from Schiffman *et al.*, 1998

or PROP (6-n-propylthiouracil) at low concentrations find bitter compounds to taste stronger than those who are insensitive to the taste of these compounds (Schiffman *et al.*, 1994). The relative degree of suprathreshold loss is also a function of the chemical structure of the tastant, especially for sweeteners (Schiffman *et al.*, 1981) and amino acids (Schiffman and Clark, 1980). For example, there is a greater degree of age-related loss for high potency sweeteners (e.g. thaumatin) compared to sucrose. For amino acids, losses in suprathreshold taste intensity are greatest for glutamic acid and aspartic acid. The ability to discriminate intensity differences between various concentrations of a tastant is also diminished in old age (Schiffman, 1993; Schiffman and Wedral, 1996; Gilmore and Murphy, 1989). Some of these decrements in suprathreshold intensity perception may be a consequence of the marked losses in regional taste sensitivity that occur over different areas of the tongue in the elderly (Matsuda and Doty, 1995; Bartoshuk *et al.*, 1987).

B. SMELL

A diversity of molecular types can produce odors but most are non-ionic volatile compounds with molecular weights of less than 300. In persons with a normal sense of smell, odorous molecules can be perceived and discriminated from one another at micro-, nano- and sometimes picomolar concentrations. Most natural odors encountered in the environment are

complex mixtures of many volatile compounds. An overview of the research literature on threshold and suprathreshold odor losses suggests that aging takes a greater toll on olfaction than taste, that is, the magnitude of odor deficits is greater in the elderly than taste deficits. A cross-sectional study of persons in seven decades of life suggests that a systematic decrement in performance on multiple olfactory tasks begins around 60 years of age and becomes significantly worse in the 70s and 80s (Schiffman and Warwick, 1991). Olfactory losses diminish the appreciation of food and can potentially lead to malnutrition. These decrements also increase the risk from hazards such as leaking gas, spoiled food, and smoke.

1. Losses of smell at threshold concentrations

Significant elevation of detection and recognition thresholds for a broad range of food odors and other volatile compounds has been found in most odor threshold studies in the elderly (Schiffman, 1979; Cain and Gent, 1991; Doty *et al.*, 1989). For example, elevated thresholds have been reported for n-butanol (Kimbrell and Furchtgott, 1963), coal gas (Chalke and Dewhurst, 1957; Chalke *et al.*, 1958), coffee and citral (Megighian, 1958), food odors including cherry, grape, and lemon (Schiffman, 1979), menthol (Murphy, 1983), pyridine and thiophene (Perry *et al.*, 1980), 18 purified odorants (Venstrom and Amoore, 1968), and citralva (Schiffman and Warwick, 1991). In general, the odor thresholds for elderly persons are 2 to 15 times higher than for a younger cohort. Olfactory losses at threshold (and suprathreshold) levels are exacerbated by malnutrition and wasting; in some sick elderly, the sense of smell is totally absent (Schiffman and Wedral, 1996). Cognitive deficits do not necessarily impair the ability to detect odors relative to age-matched controls until fairly advanced stages of dementia. In Parkinson's disease, for example, losses in olfactory detection are independent of cognitive status (Doty *et al.*, 1989).

2. Loss of smell at suprathreshold concentrations

Suprathreshold odor perception (Schiffman, 1977, 1979; Murphy, 1983; Schiffman and Warwick 1991; Stevens and Cain, 1985) and the chemesthetic sense in the nose (e.g. CO_2 puffed into the nose stimulates the nasal branch of the trigeminal nerve) (Stevens *et al.*, 1982) are both diminished in elderly persons. Suprathreshold olfactory losses have been quantified using several methodological approaches including magnitude estimation, identification, and discrimination studies. Magnitude estimation experiments, in which numbers are assigned to odors in proportion to their

perceived intensities, suggest that the elderly perceive suprathreshold odors to be half as intense as their younger counterparts. Magnitude estimates reveal losses for pleasant (benzaldehyde and d-limonene), foul (pyridine), and neutral (ethyl alcohol and isoamyl alcohol) odorants (Stevens and Cain, 1985). Similar losses using magnitude estimation have been reported for isoamyl butyrate (Stevens *et al.*, 1982, 1984; Stevens and Cain, 1985), menthol (Murphy, 1983), eight odorants including citralva, geraniol, citronellal, 2-methoxy-3-isobutyl-pyrazine, benzaldehyde, 2-methoxypyrazine, acetic acid (Schiffman and Warwick, 1991), and CO_2 which stimulates the trigeminal nerve (Stevens *et al.*, 1982).

Losses in the ability to identify odors are especially impaired, even in healthy elderly persons (Schiffman, 1979; Doty, 1991) but there is heterogeneity among individuals (Wysocki and Gilbert, 1989). Losses have been found in the ability to identify coffee, peppermint, coal tar, and oil of almonds (Anand, 1964), foods (Murphy, 1985; Schiffman, 1977), steroids (Schiffman, 1979), 40 common substances (Schemper *et al.*, 1981), and a microencapsulated battery of 40–50 odors (Doty *et al.*, 1984). Scores for healthy elderly persons over 70 years of age are generally 60% to 75% of those for young subjects. More than 75% of elderly persons over 80 have major difficulty perceiving and identifying odors (Doty, 1991). Odor identification is especially impaired in Alzheimer's disease (see section below on Diseases that Affect the Senses of Taste and Smell) and in patients with other neurodegenerative diseases (Doty, 1991; Schiffman *et al.*, 1990a). This is not surprising since odor identification is a cognitively demanding task which requires retrieval of verbal labels from memory.

Multidimensional scaling (MDS) experiments in which odors are arranged in a space on the basis of their perceived similarities indicate that the elderly have reduced capacity to discriminate the degree of difference between odors of different qualities (Schiffman, 1979; Schiffman and Warwick, 1991). MDS experiments have found losses in discrimination for food odors (Schiffman and Pasternak, 1979), common odors (Stevens and Lawless, 1981), and pyrazines (Schiffman and Leffingwell, 1981).

IV. DISEASES THAT AFFECT THE SENSES OF TASTE AND SMELL

A broad range of medical conditions have been reported to induce taste and smell losses (see Tables IX and X). Some of the olfactory losses reported in elderly individuals may have arisen from medical conditions that occurred earlier in their lives such as nasal and/or sinus disease, upper respiratory infections, and head trauma. Nasal and/or sinus disease can block access of odorants to the olfactory epithelium or cause damage to

TABLE IX

MEDICAL CONDITIONS THAT HAVE BEEN REPORTED TO AFFECT THE SENSE OF TASTE

Classification/Condition	Type of study	# of subjects in study	Problem	Source
Nervous				
Alzheimer's disease	Experiment	66/human	Loss in ability to detect glutamic acid	Schiffman *et al.*, 1990a
Bell's palsy	Clinical observation	34 of 41/human	Impairment of taste	Ekstrand, 1979
Damage to chorda tympani	Clinical observation	34/human	Ageusia	Jeppsson & Hallen, 1971
Guillain-Barre syndrome	Clinical observation	2/human	Ageusia/dysgeusia	Soria *et al.*, 1990
Familial dysautonomia	Experiment (drop technique)	6/human	Hypogeusia; absence of fungi-form & circumvallate papillae	Henkin & Kopin, 1964
Head trauma	Experiment (drop technique)	29/human	Hypogeusia & dysgeusia	Schechter & Henkin, 1974
Multiple sclerosis	1. Experiment 2. Case study	1. 79/human 2. 1/human	1. Hypogeusia (for NaCl & QHCl) 2. Episodic odd taste in mouth; loss of taste	1. Catalanotto *et al.*, 1984 2. Cohen, 1964
Raeder's paratrigeminal syndrome	Clinical observation	3/human	Dysgeusia	Fisher, 1971
Tumors and lesions	1. Clinical observation 2. Clinical observation	1. 1/human 2. 1/human	1. Localized dysgeusia 2. Central disturbance of taste	1. El-Deiry & McCabe, 1990 2. Nakajima *et al.*, 1983

TABLE IX *(continued)*

MEDICAL CONDITIONS THAT HAVE BEEN REPORTED TO AFFECT THE SENSE OF TASTE

Classification/Condition	Type of study	# of subjects in study	Problem	Source
Nutritional				
Cancer	1. Experiment 2. Experiment (drops on mid-dorsum of tongue)	1. 50/human 2. 50/human	1. Elevated sweet threshold & lowered bitter threshold 2. Higher RT for sucrose & lower RT for urea	1. DeWys & Walters, 1975 2. Gallagher & Tweedle, 1983
Chronic renal failure	Experiment	43/human	Higher recognition thresholds	Ciechanover *et al.*, 1980
Liver disease including cirrhosis	1. Experiment (drop technique) 2. Experiment (drop technique) 3. Experiment (drop technique)	1. 8/human 2. 37/human 3. 38/human	1. Decrease in acuity (increase in DT for NaCl and urea, and in RT for urea) 2. Hypogeusia 3. Hypogeusia	1. Burch *et al.*, 1978 2. Garrett-Laster *et al.*, 1984 3. Smith *et al.*, 1976
Niacin (vitamin B_3) deficiency	Clinical observation	—	Hypogeusia	Green, 1971
Thermal burn	Experiment (drops technique)	16 of 19/human	Hypogeusia or ageusia	Cohen *et al.*, 1973
Zinc deficiency	Experiment	6/human	Hypogeusia	*Nutr. Rev.*, 1978

TABLE IX *(continued)*

MEDICAL CONDITIONS THAT HAVE BEEN REPORTED TO AFFECT THE SENSE OF TASTE

Classification/Condition	Type of study	# of subjects in study	Problem	Source
Endocrine				
Adrenal cortical insufficiency	Experiment (drop technique)	—/human	Hypergeusia (very low DT, but higher than normal RT)	Henkin, 1975
Congenital adrenal hyperplasia	Experiment (drop technique)	—/human	Hypergeusia (very low DT, but higher than normal RT)	Henkin, 1975
Cretinism	Experiment	27/human	Higher incidence of nontasters of PTC	Shepard & Gartler, 1960
Cushing's syndrome	Experiment (drop technique)	—/human	Hypogeusia	Henkin, 1975
Panhypopituitarism	Experiment (drop technique)	—/human	Hypergeusia (very low DT, but higher than normal RT)	Henkin, 1975
Hypothyroidism	1. — 2. Experiment	1. — 2. 18/human	1. — 2. Hypogeusia	1. Schaupp & Seilz, 1969 2. McConnell *et al.*, 1975
Diabetes mellitus	Experiment	9/human	Impaired ability to detect glucose	Halter *et al.*, 1975
Gonadal dysgenesis (Turner's syndrome)	Clinical observation (drop technique)	9/human	Hypogeusia for sour and bitter tastes	Henkin, 1967
Pseudohypoparathyroidism	Clinical observation (drop technique)	6/human	Hypogeusia for sour and bitter tastes	Henkin, 1968

TABLE IX *(continued)*
MEDICAL CONDITIONS THAT HAVE BEEN REPORTED TO AFFECT THE SENSE OF TASTE

Classification/Condition	Type of study	# of subjects in study	Problem	Source
Local				
Facial hypoplasia	Clinical observation	5/human	Decrease in recognition sensitivity	Henkin *et al.*, 1966
Glossitis and other oral disorders	1. Case study 2. Clinical observation	1. 1/human 2. 48 of 54/human	1. Dysgeusia 2. Dysgeusia	1. Brenner & Simon, 1984 2. Johansson *et al.*, 1984
Leprosy	Experiment	12 of 30/human	Mild to severe hypogeusia	Soni & Chatterji, 1981
Oral Crohn's disease	Clinical observation	2/human	Metallic dysgeusia	Frankel *et al.*, 1985
Radiation therapy	1. Clinical observation 2. Clinical observation	1. 9/human 2. 1/human	1. Hypogeusia/dysgeusia 2. Hypogeusia/dysgeusia	1. Conger, 1973 2. Kalmus & Farnsworth, 1959
Sjogren's syndrome	Experiment (drop technique)	29/human	Hypogeusia	Henkin *et al.*, 1972
Viral and infectious				
Influenza-like infections	Experiment (drop technique)	87/human	Hypogeusia with & without dysgeusia; pathological changes in taste buds	Henkin *et al.*, 1975

TABLE IX *(continued)*

MEDICAL CONDITIONS THAT HAVE BEEN REPORTED TO AFFECT THE SENSE OF TASTE

Classification/Condition	Type of study	# of subjects in study	Problem	Source
Other				
Amyloidosis and sarcoidosis	1. Clinical observation 2. Clinical observation	1. 2/human 2. 1/human	1. Taste dysfunction 2. Ageusia	1. Schellinger *et al.*, 1983 2. Ujike *et al.*, 1987
Cystic fibrosis	1. Experiment 2. Experiment (drop technique)	1. 2 of 16/human 2. 10 of 11/human	1. Hypergeusia 2. Hypergeusia	1. Desor & Maller, 1975 2. Henkin & Powell, 1962
High altitude	Clinical observation	1/human	Ageusia	Kassirer & von Pelejo Such, 1989
Hypertension	1. Experiment 2. Experiment	1. 20/human 2. 17/human	1. Higher NaCl thresholds 2. Higher NaCl thresholds	1. Fallis *et al.*, 1962 2. Viskoper & Lugassy, 1979
Laryngectomy	Clinical observation (drop technique)	123/human	Hypogeusia	Kashima & Kalinowski, 1979
Major depressive disorder	Experiment	36/human	Altered sensitivity to supra-threshold concentrations of sucrose	Amsterdam *et al.*, 1987

TABLE X

MEDICAL CONDITIONS THAT HAVE BEEN REPORTED TO AFFECT THE SENSE OF SMELL

Classification/ condition	Source	Type of study	# of subjects	Problem
Nervous				
Alzheimer's disease	1. Moberg *et al.*, 1987 2. Schiffman *et al.*, 1990a 3. Serby *et al.*, 1985a,b	1. Experiment 2. Experiment 3. Experiment	1. 42/human 2. 66/human 3. 11/human	1. Poor odor recognition memory 2. Loss in ability to recognize odorants 3. Hyposmia
Down's syndrome	Warner *et al.*, 1988	Experiment	9/human	Low U PENN SIT scores
Epilepsy	Currie *et al.*, 1971	Clinical	80 of 666/human	Phantosmia/dysosmia related to attack
Head trauma	1. Leigh, 1943 2. Levin *et al.*, 1985 3. Moran *et al.*, 1985 4. Schechter & Henkin, 1974 5. Sumner, 1964	1. Clinical observation 2. Experiment 3. Clinical observation 4. Experiment 5. Clinical observation	1. 72/human 2. 52/human 3. 2/human 4. 29/human 5. 87 of 1167/human	1. Anosmia, hyposmia, or parosmia 2. Olfactory naming and recognition impairment 3. Anosmia 4. Hyposmia & dysosmia 5. Anosmia
Korsakoff's syndrome	1. Jones *et al.*, 1975 2. Mair *et al.*, 1986	1. Experiment 2. Experiment	1. 14/human 2. 8/human	1. Severe impairment of olfactory discrimination 2. Smell identification deficit
Migraine	1. Crosley & Dhamoon, 1983 2. Wolberg & Ziegler, 1982	1. Clinical observation 2. Clinical observation	1. 2/human 2. 1/human	1. Phantosmia 2. Olfactory hallucination
Multiple sclerosis	Pinching, 1977	Clinical observation	22/human	Hyposmia or anosmia

TABLE X *(continued)*

MEDICAL CONDITIONS THAT HAVE BEEN REPORTED TO AFFECT THE SENSE OF SMELL

Classification/ condition	Source	Type of study	# of subjects	Problem
Nervous				
Parkinson's disease	1. Ansari & Johnson, 1975 2. Doty *et al.*, 1988 3. Serby *et al.*, 1985a,b 4. Ward *et al.*, 1983	1. Experiment 2. Experiment 3. Experiment 4. Experiment	1. 10 of 22/ human 2. 81/human 3. 11/human 4. 72/human	1. Decrease in olfactory acuity (increase in DT for amyl acetate) 2. Decrements in olfactory tests 3. Hyposmia 4. Hyposmia
Tumors and lesions	1. Bakay, 1984 2. Furstenberg et al., 1943 3. Jarus & Feldon, 1982 4. Olsen & DeSanto, 1983	1. Clinical observation 2. Clinical observation 3. Clinical observation 4. Clinical observation	1. 29/human 2. — 3. 1/human 4. 21/human	1. Complete to partial (unilateral) anosmia 2. Smell disturbances 3. Anosmia 4. Anosmia
Nutritional & metabolic				
Chronic renal failure	Schiffman *et al.*, 1978	Experiment	11/human	Reduced olfactory discrimination
Liver disease including cirrhosis	1. Burch *et al.*, 1978 2. Garrett-Laster *et al.*, 1984	1. Experiment 2. Experiment	1. 8/human 2. 37/human	1. Decrease in acuity (increase in DT for 3 odors and in RT for 2 odors) 2. Hyposmia
Trimethylaminuria	Leopold *et al.*, 1990	Clinical observation	1/human	Dysosmia
Vitamin B_{12} deficiency	Rundles, 1946	Clinical observation	4 of 20/human	Hyposmia, anosmia, or dysosmia

TABLE X *(continued)*

MEDICAL CONDITIONS THAT HAVE BEEN REPORTED TO AFFECT THE SENSE OF SMELL

Classification/ Condition	Source	Type of study	# of subjects	Problem
Endocrine				
Adrenal cortical insufficiency	Henkin, 1975	Experiment	—/human	Hyperosmia
Cushing's syndrome	Henkin, 1975	Experiment	—/human	Hyposmia
Hypothyroidism	1. McConnell *et al.*, 1975 2. Schaupp & Seilz, 1969	1. Experiment 2. —	1. 18/human 2. —	1. Hyposmia 2. —
Diabetes mellitus	Jorgensen & Buch, 1961	Experiment	58/human	Hyposmia & anosmia
Gonadal dysgenesis (Turner's syndrome)	Henkin, 1967	Clinical observation	9/human	Hyposmia
Hypogonadotropic hypogonadism (Kallman's syndrome)	1. Kallmann *et al.*, 1944 2. Males *et al.*, 1973	1. Clinical observation 2. Clinical observation	1. Affected members of 3 families 2. 6/human	1. Anosmia 2. Anosmia
Primary amenorrhea	Marshall & Henkin, 1971	Experiment	96/human	Hyposmia
Pseudo-hypoparathyroidism	1. Henkin, 1968 2. Weinstock *et al.*, 1986	1. Clinical observation 2. Experiment	1. 6/human 2. 5/human	1. Hyposmia 2. Hyposmia
X-linked ichthyosis due to steroid sulfatase deficiency	1. Andria *et al.*, 1987 2. Sunohara *et al.*, 1986	1. Clinical 2. Case study	1. 2/human 2. 3/human	1. Anosmia 2. Anosmia

TABLE X *(continued)*

MEDICAL CONDITIONS THAT HAVE BEEN REPORTED TO AFFECT THE SENSE OF SMELL

Classification/ Condition	Source	Type of study	# of subjects	Problem
Local				
Adenoid hypertrophy	Ghorbanian *et al.*, 1978	Experiment	48/human	Hyposmia
Allergic rhinitis, atopy, and bronchial asthma	1. Church *et al.*, 1978 2. Fein *et al.*, 1966	1. Clinical observation 2. Clinical observation (self-report)	1. 54/human 2. 18/human	1. Hyposmia 2. Anosmia
Crouzon's syndrome	Das & Munro, 1979	Case study	2/human	Anosmia
Facial hypoplasia	Henkin *et al.*, 1966	Clinical observation	5/human	Hyposmia
Leprosy	Barton, 1974	Experiment	57 of 150/human	Some degree of hyposmia
Ozena	Strandbygard, 1954	Clinical observation	10/human	Pathological olfactory mucosa
Paranasal sinus exenteration	Hoye *et al.*, 1970	Clinical observation	17/human	Hyposmia
Sinusitis and polyposis	1. Fein *et al.*, 1966 2. Hotchkiss, 1956 3. Ryan & Ryan, 1974	1. Clinical observation (self-report) 2. Clinical observation 3. Clinical observation	1. 18/human 2. 30/human 3. —	1. Anosmia 2. Most w/anosmia 3. Parosmia & anosmia
Sjogren's syndrome	Henkin *et al.*, 1972	Experiment	29/human	Hyposmia

TABLE X *(continued)*

MEDICAL CONDITIONS THAT HAVE BEEN REPORTED TO AFFECT THE SENSE OF SMELL

Classification/ condition	Source	Type of study	# of subjects	Problem
Viral and infectious				
Acute viral hepatitis	Henkin & Smith, 1971	Clinical observation	19/human	Hyposmia
HIV infection	Brody *et al.*, 1991	Experiment	42/human	Hyposmia
Influenza-like infections	Henkin *et al.*, 1975	Experiment	87/human	Hyposmia with & without dysosmia; pathological changes in nasal mucous membranes
Other				
Amyloidosis and sarcoidosis	1. Delaney *et al.*, 1977 2. Schellinger *et al.*, 1983	Clinical observation	1. 5/human 2. 2/human	1. Hyposmia due to damage to the CNS 2. Smell dysfunction
Cystic fibrosis	1. Henkin & Powell, 1962 2. Hertz *et al.*, 1975	1. Experiment 2. Experiment	1. 9 of 11/human 2. 19/human	1. Hyperosmia 2. Hyposmia
Familial (genetic)	Singh *et al.*, 1970	Clinical observation	6 of 1 family/human	Anosmia
Laryngectomy	1. Henkin *et al.*, 1968 2. Henkin & Larson, 1972	1. Clinical observation 2. Clinical observation	1. 35/human 2. 2 of 4/human	1. Hyposmia 2. Hyposmia
Psychiatric disorders	Meats, 1988	Clinical observation	—	Olfactory hallucinations

receptors and olfactory pathways (Doty and Snow, 1987). Losses of olfactory sensations that occur after upper respiratory infections probably result from direct damage to the olfactory epithelium and replacement of the olfactory epithelium with respiratory epithelium (Douek *et al.*, 1975); olfactory cilia may be damaged as well (Jafek *et al.*, 1989). Anosmia subsequent to head trauma is thought to result from the shearing of olfactory nerve fibers as they course through the cribriform plate. Post-traumatic olfactory dysfunction has also been correlated with damage to the olfactory bulbs and tracts and the inferior frontal lobes (Yousem *et al.*, 1996). Aside from nasal disease, respiratory infections, and head trauma, the mechanisms by which diseases alter olfactory perception are not well understood.

Two chronic medical conditions in which the incidence of taste and/or smell disorders is especially high are cancer and Alzheimer's disease (AD). Both of these conditions disproportionately impact the elderly. Most AD patients are over the age of 65 years (Blacker *et al.*, 1997), and 60% of persons diagnosed with cancer are 65 years and older (Cohen, 1998), while 69% of all cancer deaths occur in persons over 65 years of age.

A. CANCER

Altered taste and smell functioning have been found in untreated patients (Ovesen *et al.*, 1991; Brewin, 1980) as well as patients treated with radiation (Conger, 1973), chemotherapy (Nielsen *et al.*, 1980; Lindley *et al.*, 1996; Fetting *et al.*, 1985), and immunotherapy (unpublished data, Schiffman, 1999). An overview of the chemosensory changes that have been observed in a variety of cancer types is given in Table XI. Altered preferences and complaints in cancer patients are shown in Table XII. The data indicate that cancer and its treatment impair the ability to detect the presence of basic tastes, reduce the perceived intensity of suprathreshold concentrations of tastants, and interfere with the ability to discriminate and identify tastes and odors. Fifty per cent or more of cancer patients may have impaired taste and smell functioning at some point during the course of their disease and treatment (DeWys and Walters, 1975). The time course of recovery (if any) varies over individuals with the duration of losses ranging from several weeks to six months or longer (Mossman *et al.*, 1982; Conger, 1973; Ophir *et al.*, 1988).

The causes of altered taste and smell functioning in cancer are not well understood but metabolic changes induced by the neoplasm itself or injury to the sensory receptors by therapies are likely involved. Chemotherapy and radiation therapy may also interfere with the turnover of taste and

TABLE XI

CHANGES IN THRESHOLD, INTENSITY, DISCRIMINATION, AND IDENTIFICATION TASKS IN CANCER PATIENTS

Type of cancer	Effect of therapy	Threshold loss	No. of patients	Reference
Various malignant neoplams	Radiotherapy further impaired taste loss	Elevated detection and recognition thresholds for NaCl (salt), sucrose (sweet), HCl (sour) and urea (bitter) prior to radiotherapy; salty, sweet, and bitter further impaired by radiotherapy	35	Bolze *et al.*, 1982
Oropharyngeal cancers	Radiotherapy	Elevated recognition thresholds for sucrose (sweet), HCl (sour), quinine HCl (bitter) during radiotherapy; recovery by 120 days	8	Conger, 1973
Head and neck	Radiotherapy	Elevated detection and recognition thresholds, especially for bitter and salt thresholds during radiotherapy	13	Mossman and Henkin, 1978
Breast and colon	Prior to treatment	Elevated NaCl (salty) recognition thresholds	48	Carson and Gormican, 1977
Lung	Prior to therapy	Elevated recognition threshold for hydrochloric acid (sour); individual differences in bitter and sweet threshold changes	30	Williams and Cohen, 1978
Oropharyngeal	During and after radiotherapy	Elevated taste recognition thresholds for NaCl, sucrose, quinine sulfate, picric acid; thresholds returned to normal 6 weeks post-treatment	1	Kalmus and Farnsworth, 1959

TABLE XI *(continued)*

CHANGES IN THRESHOLD, INTENSITY, DISCRIMINATION, AND IDENTIFICATION TASKS IN CANCER PATIENTS

Type of cancer	Effect of therapy	Threshold loss	No. of patients	Reference
Oral squamous cell carcinoma	Radiation and chemotherapy	Thresholds for NaCl (salt), tartaric acid (sour), sucrose (sweet), and quinine (bitter) elevated by radiation and chemotherapy; recovery was not complete by 1 year	41	Tomita and Osaki, 1990
Various malignant neoplasms	During chemotherapy	Elevated glucose recognition threshold	36	Bruera *et al.*, 1984
Lung, ovary, breast	Increase in untreated patients; thresholds decreased only in patients who responded to chemotherapy (after 2 to 3 months)	Significant increase in electrical taste detection threshold; no change in smell threshold	51	Ovesen *et al.*, 1991
Gastrointestinal		Significant decrease in recognition threshold for urea (bitter)	30	Hall *et al.*, 1980
Melanoma	During 9 courses of chemotherapy	Loss of ability to discriminate between different concentrations of salt, sweet, sour, and bitter		Mulder *et al.*, 1983
Breast cancer	Mixed sample (treated and untreated)	Significant reduction in smell identification in patients with estrogen-receptor positive breast cancer	46	Lehrer *et al.*, 1985

TABLE XII

ALTERED PREFERENCES AND PATIENT COMPLAINTS

Type of cancer	Effect of therapy	Sensory loss	No. of patients	Reference
Various malignant neoplasms	Radiotherapy	Food aversions and cravings	147	Brewin, 1980
Various	Treated and untreated	Reduced palatability of high-protein foods, cereals, sweets in patients with taste aversions	111	Vickers *et al.*, 1981
Oropharyngeal	Developed during first two weeks of radiotherapy	All food tasted nauseating, greasy or rancid; wine tasted metallic; water tasted salty	1	Kalmus and Farnsworth, 1959
Breast and lung	Prior to and during chemotherapy	Patients developed aversions to sweets, meats, caffeinated beverages, high fat and greasy foods during therapy	76	Mattes *et al.*, 1987
28 types including breast, colorectal, Hodgkin's, lung, lymphoma	No difference between patients treated or untreated with chemotherapy	Patients who reported food aversions rated food samples of chocolate, ham, pork, roast beef and chicken as less pleasant	133	Nielsen *et al.*, 1980
Various		Symptom of reduced appetite correlates with elevated recognition threshold for sucrose (sweet); meat aversion correlates with lowered thresholds for urea (bitter)	50	DeWys and Walters, 1975

TABLE XII *(continued)*

ALTERED PREFERENCES AND PATIENT COMPLAINTS

Type of cancer	Effect of therapy	Sensory loss	No. of patients	Reference
Upper gastrointestinal; lung	Patients on chemotherapy had less distinct preference for any of the 5 concentrations of sucrose, particularly high levels	Highly varied hedonic responses to beverages containing 5 suprathreshold concentrations of citric acid (in lemonade), NaCl (in unsalted tomato juice), urea (in tonic water), and sucrose (in cherry drink); anorectics preferred lower sweetness levels than nonanorectics; yet sweet foods constituted a greater percentage of their daily caloric intake	62	Trant *et al.*, 1982
Head and neck cancer	During radiotherapy	Percentage of patients reporting taste problems increased from 18% prior to radiation to over 80% during the 5th week of radiation; foods with abnormal taste included high protein foods (meat, eggs, dairy), fruits, vegetables, sweets, breads, cereal, coffee, tea	74	Chencharick and Mossman, 1983
Breast, lung	Chemotherapy-cisplatin	Complaints of metallic, bitter, or decreased taste; distorted sweet taste; changes in odor of food, especially unpleasantness; increased sensitivity to odors such as perfumes and hospital odors	44	Rhodes *et al.*, 1994

smell receptors. Oral complications experienced by cancer patients such as infections (fungal, viral, bacterial), ulcers, drug-induced stomatitis, and dry mouth may also play a role.

Unpleasant taste and smell sensations are one of the main causes of food aversions reported by cancer patients. Food aversions can also be learned during the course of cancer when sensory properties of foods are associated with gastrointestinal distress (e.g. nausea) of therapy (Andrykowski and Otis, 1990; Bernstein and Bernstein, 1981). Learned food aversions often persist long after all symptoms of discomfort have subsided.

B. ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a genetically heterogeneous and progressive degenerative disorder of the brain characterized by progressive memory loss and deteriorating cognitive functioning (Shastry, 1998). Losses in the ability to recognize, identify, and remember odorants are salient in the earliest phases of AD and are substantially worse than in age-matched controls. An overview of chemosensory studies of AD suggests that the size of olfactory deficits is related to the degree of dementia (Larsson *et al.*, 1999). In 1974, Waldton performed both a cross-sectional and longitudinal study of olfaction in patients with AD. He found diminished ability to identify the odor of tinctura asa foetida, camphor, citrus fruit, eau de cologne, menthol, and petrol. Subsequent studies have reported similar findings. Peabody and Tinklenberg (1985) found that AD patients had reduced ability to smell and identify strong odors (lemon, peppermint, coffee, maple, and vinegar) or select the correct identity of odors from a list. Alzheimer's patients also displayed less ability than age-matched controls on a 10-pair forced-choice identification task in which the patient was asked to choose which of two vials contained the odor named by the experimenter (Serby *et al.*, 1985a, b; Serby, 1986, 1987). The 10 odor pairs tested in this experiment were: garlic–onion, lemon–orange, water–pineapple, chocolate–maple, bacon–curry, rose–vanilla, coffee–peanuts, vinegar–soap, cinnamon–licorice, and ketchup–mint.

Knupfer and Spiegel (1986) found that Alzheimer's patients had difficulty determining if the second stimulus of an odor pair was identical to the first one. Pairs of different, similar, and identical odors were presented including: coconut–cloves, eucalyptus–smoked bacon, aniseed–orange, rum–licorice, asparagus–pine needles, moth balls–camphor, marzipan–bitter almond, grass–hay, lemon–flower, and peppermint–spearmint. Knupfer and Speigel's AD patients were also asked to choose which of two vials contained an odor named by the experimenter, and again they performed poorly. Performance on a standardized scratch and

sniff test containing 36–40 odors impregnated in tapes was also impaired in AD patients (Warner *et al.*, 1986; Koss *et al.*, 1987, 1988; Kesslak *et al.*, 1988; and Doty *et al.*, 1987). Rezek (1987) also found that patients with AD performed poorly when they were asked to smell and identify cinnamon oil, lemon oil, peppermint oil, turpentine, and ground coffee and select the name of the odor from a 10-item list. Thus, there is considerable agreement among these studies that the ability to recognize and identify odors in AD is impaired.

Patients with AD also perform poorly on odor memory tasks. This was demonstrated by Moberg *et al.* (1987) who first presented AD patients with 10 target odors including onion, vanilla, almond, peppermint, lemon, cinnamon, pine, mothballs, smoke, and banana. Five minutes later, 20 odorants were presented – the original 10 target odors plus five distractants (odors similar to the original five odorants), and five dissimilar odors. The subject was asked to determine if any of the 20 odorants were the same as the original 10. Kesslak *et al.* (1988) also found poor olfactory memory in AD patients on an odor match to sample test. One of 15 uncommon odors (target) was followed by three "choice" odors. The task was to choose which of the three "choice" odors matched the target.

The data regarding altered olfactory functioning at threshold concentrations in Alzheimer's disease are more equivocal. Three studies have found little or no threshold losses in early AD (St Clair, 1985; Rezek, 1987; Koss *et al.*, 1987, 1998). On the other hand, three other studies have reported losses. Knupfer and Spiegel (1986) determined thresholds with a three-bottle forced-choice procedure in which one bottle contained the odor plus solvent and the other two bottles contained only solvent. He found threshold losses for eucalyptol, citral, and prunolide (coconut). Doty *et al.* (1987) found that patients with mild to moderate AD had a threshold loss for the odor of phenyl ethyl alcohol using a single-staircase, forced-choice procedure. Murphy *et al.* (1987) reported a loss for butanol in AD using a two-alternative, forced-choice ascending series. Murphy *et al.* (1990) concluded that degree of elevation of olfactory thresholds in patients with Alzheimer's disease appears to reflect the effects of the disease process. Taste losses to glutamic acid have also been reported in AD (Schiffman *et al.*, 1990a). It should be noted, however, that taste and smell losses are also found in demented patients without AD (Schiffman *et al.*, 1990a).

Anatomic and physiological changes that occur during normal aging are especially profound in neurodegenerative diseases such as Alzheimer's disease (Doty, 1991). The sensory decrements in Alzheimer's disease result from histopathological and neurochemical changes in the olfactory epithelium (Talamo *et al.*, 1989), olfactory bulb (Ohm and Braak, 1987),

anterior olfactory nucleus (Averback, 1983; Ohm and Braak, 1987), olfactory tubercle (Simpson *et al.*, 1984), amygdala (Brun and Gustafson, 1976), prepyriform cortex (Reyes *et al.*, 1987), hippocampus (Brun and Gustafson, 1976; Hyman *et al.*, 1984); entorhinal cortex (Brun and Gustafson, 1976; Hyman *et al.*, 1984), uncus (Brun and Gustafson, 1976), and subiculum (Hyman *et al.*, 1984). The histopathological changes in these olfactory projection areas include neuritic plaques, neurofibrillary tangles, and granulovacuolar degeneration. Altered neurotransmitter levels may also play a role in the olfactory losses associated with AD (Francis *et al.*, 1999). Early olfactory losses (memory, identification) are presumed to be due to physiological changes of the central nervous system such as the limbic system rather than being peripheral in origin. Later deficits (e.g. threshold losses) are presumed to include peripheral physiological changes.

Genetic factors also appear to play a role in olfactory sensitivity in AD and are currently being used to predict who will get AD. For example, genetic studies have established a link between the apolipoproteinE (apoE) gene found on chromosome 19 and the development of AD (Strittmatter *et al.*, 1993; Roses and Saunders, 1994). Inheritance of one of the three forms of the apoE gene, the E4 form, conferred a genetic risk, which may account for 60–80% of early onset AD. In one study, persons with the apoE4 allele showed significantly poorer odor identification than those without an E4 allele (Murphy *et al.*, 1998; Bacon *et al.*, 1998). The E2 form of the gene is apparently protective against AD while apoE3 is the most common. Recent data suggest that people who inherit an apoE2 gene with an apoE3 gene (each individual inherits two apoE genes, one from each parent) develop AD 20 years later on average than people who inherit two E4 genes. Persons with the apoE4-E4 combination develop AD at about 68 years of age on average while those with E2-E3 are not afflicted till about 90 years of age (see Baker, 1994). Less than one third of the population has one apoE4 gene with 1–2% possessing the apoE4-E4 combination. However, not everyone with the apoE4 gene gets AD which suggests that there are other risk factors.

Finding methods to compensate for chemosensory losses in patients with AD is important from the public health standpoint. Currently, four million Americans suffer from Alzheimer's disease (AD); 10% of Americans over 65 years of age have AD, and 50% of people over 85 years are afflicted. By 2020, it is estimated that 14 million Americans will be affected by the disease. The average life span after onset of dementia is eight years. Currently, 50% of the 1.8 million persons in nursing homes in the United States suffer from AD or other cognitive disorders (Wall Street Journal, 1998).

V. EFFECT OF MEDICATIONS ON TASTE AND SMELL

Adverse drug reactions including chemosensory disorders occur at a higher rate in older individuals (Straand and Rokstad, 1999; Atkin and Shenfield, 1995; Stricker *et al.*, 1996). Both clinical reports and experimental studies have reported adverse taste and smell side effects from medications. Many medications have unpleasant tastes or odors of their own; in addition, drugs can alter the sensations of other chemosensory stimuli including foods and beverages (Schiffman *et al.*, 1983; Schiffman *et al.*, 1999a,b,c; Zervakis *et al.*, 2000; Schiffman *et al.*, 2000a,b,c). The exaggerated burden of drug-induced chemosensory disorders in a geriatric population is illustrated by a study of 87 persons with taste loss due to terbinafine and 362 controls on terbinafine without taste loss (Stricker *et al.*, 1996). Patients 65 years of age or more were 4.4 times more likely to develop taste loss to terbinafine than those younger than 35 years of age. Elevated frequency of chemosensory disorders in the elderly is also due to the disproportionate use of prescription and nonprescription drugs by older individuals. An overview of data on prescription drug usage in the United States and United Kingdom indicates that the elderly account for 25–39% of the prescription drug costs and up to 40% of nonprescription drugs dispensed; yet the elderly account for only 10–18% of the population (Atkin *et al.*, 1999). Community-dwelling elderly over the age of 65 take an average of 2.9 to 3.7 medications (Lewis *et al.*, 1993), and the number increases significantly to 7.2 drugs or more for elderly living in retirement and nursing homes (Ingrid K. Lewis, PharmD, personal communication). The elderly may be more susceptible to sensory side-effects of drugs due to the extensive age-related changes in physiology relevant to drug handling that occur in this population.

Adverse side effects involving taste and smell impairments have been reported for over 250 drugs although the percentage of patients affected by each drug is not well documented (Schiffman 1983; Schiffman 1997; Physicians' Desk Reference, 1995). No single drug class appears to cause complaints of adverse side effects out of proportion with its use, but complaints occur more frequently with cardiovascular drugs, NSAIDS, and psychotropic agents due in part to their high prescription rate (Atkin *et al.*, 1999). Smith and Burtner (1994) found that 47.5% of the 131 most frequently prescribed medications for 1992, as measured by IMS America's National Prescription Audit, caused altered taste such as medication taste, unusual taste, peculiar taste, bad taste, taste perversion, metallic taste, changes in taste, and decreased taste. Furthermore, the absolute number of drugs taken by an individual patient is one of the most important predictors of adverse drug reactions (Dawling and Crome, 1989).

Neither the sites of action nor the mechanisms by which medications induce clinical taste and smell disorders is well understood. However, medications can impact taste or smell perception at several levels of the nervous system including the peripheral receptors, chemosensory neural pathways, and/or the brainstem and brain. Drugs can produce tastes of their own when they are secreted into the saliva (or build up over time in taste tissues) at concentrations that are greater than taste detection thresholds. Extensive research has shown that drugs are secreted into the saliva (Mucklow *et al.*, 1978; Kragh-Sorensen and Larsen, 1980; Paxton and Donald, 1980; Anavekar *et al.*, 1978; Levy *et al.*, 1980), and salivary levels of many drugs are high enough to exert adverse effects on taste sensations either by modifying taste transduction mechanisms or by producing a taste of their own.

Diffusion of drugs from lingual blood vessels can also activate taste receptors on the basolateral side of taste receptor cells. The fact that compounds circulating in the blood can produce tastes and smells has been well known for many years (Nor *et al.*, 1996; Matsuyama and Tomita, 1986). Intravenous taste has been used medically to measure human blood circulation time. For example, 5 ml of bitter-tasting decholin (20% dehydrocholic acid) is injected into the right cubital vein over a 10 sec period, and the latent time to produce a taste is measured (Matsuyama and Tomita, 1986). Drugs can also diffuse into the nasal mucus and potentially disrupt odor perception. The concentrations of numerous drugs have been measured in nasal secretions (Melon and Reginster, 1976; Giebel *et al.*, 1979), and the levels can be higher than that in the plasma (Tominack *et al.*, 1988; Jaehde *et al.*, 1995).

Schiffman and colleagues (Schiffman *et al.*, 1999a,b,c; Zervakis *et al.*, 2000; Schiffman et al., 2000a,b,c) have performed a series of studies to quantify the effect of topical application of 62 different drugs to the tongue to simulate the situation in which the drug is secreted into saliva. These 62 drugs had been shown previously to provoke taste complaints in clinical settings. Both threshold and suprathreshold studies in elderly subjects and young controls were performed. At a concentration four times higher than the detection threshold, subjects also rated the taste quality of the drug using 14 adjectives: overall intensity, sweet, sour, salty, bitter, metallic, cooling, hot, spicy, burning, anesthetic, astringent, medicinal, and minty/menthol. The perceived intensities of suprathreshold concentrations of NaCl, KCl, $CaCl_2$, sucrose, quinine HCl, citric acid, capsaicin (pungent), *n*-ethyl-*p*-menthane-3-carboxamide or WS-3 (menthol-like), and $FeSO_4$ (metallic) were measured before and after topical application of a weak concentration of each drug. Results of these studies along with taste complaints from clinical reports are given in Table XIII.

TABLE XIII

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
AIDS- & HIV-related therapeutic drugs: nucleosides and others												
Didanosine	PDR (Videx)	Taste perversion	24.0 ± 4.22 mM (Bitter)		↓	⇓					⇓ burn	
Lamivudine			4.36 ± 1.37 mM (Bitter)		⇓	⇓				↓	↓	
Nevirapine			n/a	↓				⇓				
Stavudine			5.99 ± 1.44 mM (Bitter)		⇑	⇓						
Zalcitabine	PDR (Hivid)	Decreased or loss of taste, taste perversion										
Zidovudine	PDR (Retrovir, Retrovir IV)	Taste perversion	2.15 ± 0.60 mM (Bitter)		⇓					↓		
AIDS- & HIV-related therapeutic drugs: protease inhibitors												
Indinavir	PDR (Crixivan)	Taste perversion	0.237 ± 0.013 mM (Bitter)					⇓	↓	⇑		⇓

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Nelfinavir			n/a				⇓	⇓			↓	
Ritonavir	PDR (Norvir)	Taste loss, taste perversion, taste abnormal	0.0702 ± 0.039 mM (Bitter)	↓	↓							
Saquinavir mesylate	PDR (Invirase)	Taste altered	0.0029 ± 0.0004 mM (Bitter)	↓				⇓ burn	⇑	⇑		
Amebicides & anthelmintics												
Metronidazole	1. Strassman *et al.*, 1970 2. Griffin, 1992 3. PDR (Metrogel-vaginal, Protostat, Flagyl IV, Flagyl)	1. Sour or bitter taste in mouth, dryness of mouth 2. Taste abnormal, taste perversion 3. Sharp, unpleasant metallic taste										
Niclosamide	PDR (Niclocide)	Bad taste in mouth										
Niridazole	Prata, 1969	Bitter sensation in mouth										

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Anesthetics												
Benzocaine (ethyl aminobenzoate)	Von Skramlik, 1963	Hypogeusia especially to bitter										
Dibucaine HCl	Von Skramlik, 1963	Hypogeusia especially to bitter										
Euprocin	Von Skramlik, 1963	Hypogeusia especially to bitter										
Lidocaine	Yamada & Tomita, 1989	Hypogeusia & abnormal bitter sensation										
Procaine HCl (Novocain)	Von Skramlik, 1963	Hypogeusia especially to bitter										
Propofol	PDR (Diprivan)	Taste perversion										
Tropacocaine	Von Skramlik, 1963	Hypogeusia & abnormal bitter sensation										
Anticholesteremic & antilipidemics												
Cholestyramine	PDR (Questran, Questran Light)	Sour taste										

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Clofibrate	Henkin, 1971	Hypogeusia										
Fluvastatin sodium	PDR (Lescol)	Alteration of taste										
Gemfibrozil	PDR (Lopid)	Taste perversion	n/a		⇓							⇑
Lovastatin	PDR (Mevacor)	Dysgeusia, alteration of taste										
Pravastatin sodium	PDR (Pravachol)	Alteration of taste										
Probucol	PDR (Lorelco)	Diminished sense of taste										
Simvastatin	PDR (Zocor)	Alteration of taste										
Anticoagulants												
Phenindione	Scott, 1960	Burning sensation on tongue & local sensitivity of the taste buds										
Antihistamines												
Chlorpheniramine Maleate	Schiffman, 1983		0.085 ± 0.02 mM (Bitter)								⇓	

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Loratadine	PDR (Claritin)	Altered taste										
Terfenadine & pseudoephedrine	PDR (Seldane-D)	Taste alterations	n/a			⇑						
Antimicrobial agents												
Amphotericin B	Rollin, 1978	Hypogeusia or ageusia w/ occasional phantogeusia										
Ampicillin	Jaffe, 1970	Hypogeusia	1.458 ± 0.392 mM (Bitter)	⇓		⇓			⇓ bitter		⇑	
Atovaquone	PDR (Mepron)	Taste perversion	n/a							⇓		
Aztreonam	PDR (Azactam)	Altered taste										
Bleomycin	Soni & Chatterji, 1985	Taste loss										
Carbenicillin Indanyl sodium	PDR (Geocillin)	Bad taste										
Cefamandole	Hodgson, 1981	Bad taste in mouth										

TABLE XIII *(continued)*
DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Cefpodoxime proxetil	PDR (Vantin)	Taste alteration										
Ceftriaxone sodium	PDR (Rocephin)	Dysgeusia										
Cefuroxime axetil	PDR (Ceftin)	Poor taste of drug										
Cinoxacin	PDR (Cinobac)	Perverse taste										
Ciprofloxacin	1. Griffin, 1992 2. PDR (Cipro, Cipro IV, Ciloxan)	1. Taste altered 2. Bad taste										
Clarithromycin	PDR (Biaxin)	Abnormal taste, taste perversion										
Clindamycin phosphate	PDR (Cleocin phosphate)	Unpleasant or metallic taste										
Clofazimine	PDR (Lamprene)	Taste disorder										
Dapsone			n/a		⇓				⇓			
Enoxacin	PDR (Penetrex)	Unusual taste	0.040 ± 0.014 mM; (Metallic, bitter)				↓		⇓			

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Ethambutol 2HCl	Rollin, 1978	Metallic phantogeusia	0.247 ± 0.055 mM; (Bitter)		⇓ bitter	↓					⇓	
Griseofulvin	Fogan, 1971	Decreased taste acuity	n/a									
Imipenem-Cilastatin sodium	PDR (Primaxin IM, Primaxin IV)	Taste perversion										
Lincomycin	Henkin, 1971	Hypogeusia										
Lomefloxacin HCl	PDR (Maxaquin)	Taste perversion	0.379 ± 0.102 mM (Bitter)						⇑	⇑		
Mezlocillin sodium	PDR (Mezlin)	Abnormal taste sensation										
Norfloxacin	PDR (Chibroxin, Noroxin)	Bitter taste										
Ofloxacin	PDR (Floxin, Floxin IV)	Dysgeusia, disturbance of taste	0.387 ± 0.155 mM; (Bitter)		⇑				⇑			

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Pentamidine Isethionate	PDR 1a. (NebuPent) 1b. (Pentam 300)	1a. Bad (metallic) taste, loss of taste 1b. Bad taste in mouth	0.062 ± 0.014 mM; (Bitter)	↓	⇓	⇓						
Piperacillin & tazobactam sodium	PDR (Zosyn)	Taste perversion										
Pyrimethamine			n/a			⇑ burn						
Rifabutin	PDR (Mycobutin)	Taste perversion										
Sulfamethoxazole			0.639 ± 0.119 mM (Sour, bitter)			↓ bitter	↑					
Trimethoprim			0.264 ± 0.118 mM (Bitter)									
Tetracyclines	1. Magnasco & Magnasco, 1985 2. Soni & Chatterji, 1976	1. Intense, offensive metallic taste 2. Produces symptoms of taste alteration	0.061 ± 0.010 mM (Sour-bitter)		↓	↑ bitter						

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Ticarcillin disodium and clavulanate potassium	PDR (Timentin)	Disturbance of taste										
Tyrothricin	Seydell & McKnight, 1948	Ageusia										
Antiproliferative, including immunosuppressive agents												
Aldesleukin	PDR (Proleukin)	Taste disorder										
Azathioprine	Rollin, 1978	Hypogeusia or ageusia with occasional phantogeusia										
Carmustine	Reyes *et al.*, 1973	Dry mouth, metallic taste										
Cisplatin	Schiffman, 1991	Dysgeusia										
Carboplatin	PDR (Paraplatin)	Change in taste										
Doxorubicin and methotrexate	1. Guthrie & Way, 1974 2. Duhra & Foulds, 1988	1. Altered taste sensation 2. Loss of taste sensation to all foods										

TABLE XIII *(continued)*
DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Fluorouracil	PDR (Efudex)	Medicinal taste										
Interferon alfa-2a (recombinant)	PDR (Roferon-A)	Change in taste										
Interferon alfa-2b (recombinant)	PDR (Intron)	Taste alteration										
Levamisole HCl (immunomodulator)	PDR (Ergamisol)	Taste perversion	0.449 ± 0.148 mM (Bitter)			⇑			↑			
Vincristine sulfate	State *et al.*, 1977	Decrease in number and content of foliate & vallate taste buds										
Antirheumatic, antiarthritic, analgesic-antipyretic, and anti-inflammatory												
Auranofin	PDR (Ridaura)	Dysgeusia										
Aurothioglucose	PDR (Solganol)	Metallic taste										
Benoxaprofen	Griffin, 1992	Taste loss, taste abnormal, taste perversion										
Butorphanol tartrate	PDR (Stadol, Stadol NS)	Unpleasant taste										

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Choline magnesium trisalicylate	PDR (Trilisate)	Dysgeusia										
Colchicine	Beidler & Smallman, 1965	Hypogeusia										
Dexamethasone	1. Fehm-Wolfsdorf *et al.*, 1989 2. PDR (Decadron)	1. Less sensitive to detection of differences 2. Taste disorder	0.0902 ± 0.024 mM (Bitter)			⇓						
Diclofenac potassium/ diclofenac sodium	PDR (Cataflam/Voltaren)	Taste disorder	1.008 ± 0.220 mM (Bitter)				↓		⇓	⇓	⇑	
Dimethyl sulfoxide	PDR (Rimso-50)	Garlic-like taste										
Etodolac	PDR (Lodine)	Taste perversion										
Fenoprofen calcium	PDR (Nalfon)	Metallic taste	1.111 ± 0.388 mM (Metallic, sour)									⇓
Flurbiprofen	PDR (Ansaid)	Changes in taste										

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
1. Gold 2. Gold sodium thiomalate	1. Rollin, 1978 2. PDR (Myochrysine)	1. Metallic phantogeusia 2. Metallic taste										
Hydrocortisone	Fehm-Wolfsdorf *et al.*, 1989	Less sensitive to detection of differences; higher detection thresholds	0.0928 ± 0.02 mM (Bitter)									
Hydromorphone HCl	PDR (Dilaudid, Dilaudid-HP)	Taste alterations										
Ibuprofen			n/a								↑ bitter	
Ketoprofen	PDR (Orudis)	Taste perversion	n/a						⇑ bitter			
Ketorolac Tromethamine	PDR (Toradol)	Abnormal taste										
Morphine sulfate	PDR (MS Contin, MSIR, Oramorph SR)	Taste alterations										
Nabumetone	PDR (Relafen)	Taste disorder	n/a	⇓	⇓	⇓ sour	↓					
Nalbuphine HCl	PDR (Nubain)	Bitter taste										

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Oxaprozin	PDR (Daypro)	Alteration in taste										
D-penicillamine & penicillamine	1. Sternlieb & Sheinberg, 1964 2. Keiser *et al.*, 1968 3. Griffin, 1992 4. PDR (Cuprimine, Depen)	1. Taste loss 2. Hypogeusia 3. Taste loss, taste abnormal 4. Blunting, diminution, or total loss of taste perception										
Pentazocine lactate	PDR (Talwin)	Taste alteration										
Phenylbutazone	Rollin, 1978	Ageusia										
Piroxicam	Griffin, 1992	Taste abnormal										
Salicylates	1. Hellekant & Gopal, 1975 2. Bourliere *et al.*, 1959	1. Hypogeusia or ageusia 2. Lower DT for quinine sulfate										
Sulindac	PDR (Clinoril)	Ageusia, metallic or bitter taste	n/a		↓							
Sumatriptan succinate	PDR (Imitrex)	Disturbance of taste										
5-Thiopyridoxine	Huskisson *et al.*, 1980	Ageusia										

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Antiseptics												
Hexetidine	Plath & Otten, 1969	Salty and burning tastes										
Antispasmodics, Irritable Bowel Syndrome												
Dicyclomine HCl	PDR (Bentyl)	Taste loss	0.0354 ± 0.010 mM; (Bitter)		⇓	⇓						
Oxybutynin	Griffin, 1992	Taste altered										
Phenobarbital + Hyoscyamine SO_4 + atropine SO_4 + Scopolamine Hydrobromide	PDR (Donnatal, & Donnatal Extentabs)	Loss of taste sense										
Antithyroid agents												
Carbimazole	Erikssen *et al.*, 1975	Ageusia										
Methimazole	1. Erikssen *et al.*, 1975 2. Hallman & Hurst, 1953 3. PDR (Tapazole)	1. Ageusia 2. Ageusia 3. Loss of taste	2.111 ± 1.07 mM; (Bitter)									

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Methylthiouracil	Schneeberg, 1952	Dysgeusia, ageusia										
Propylthiouracil	Grossman, 1953	Hypogeusia										
Thiouracil	Rollin, 1978	Hypogeusia or ageusia with occasional phantogeusia										
Antiulcerative												
Clidinium bromide	PDR (Quarzan)	Loss of taste										
Famotidine	PDR (Pepcid)	Taste disorder										
Glycopyrrolate	PDR (Robinul)	Loss of taste										
Hyoscyamine sulfate	PDR (Levsin/Levsinex)	Loss of taste										
Mesalamine	PDR (Asacol)	Taste perversion										
Misoprostol	PDR (Cytotec)	Abnormal taste										
Omeprazole	PDR (Prilosec)	Taste perversion										
Propantheline bromide	PDR (Pro-Banthine)	Loss of sense of taste										

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Sulfasalazine	Rollin, 1978	Hypogeusia or ageusia with occasional phantogeusia										
Antiviral												
Acyclovir	PDR (Zovirax)	Medication taste	n/a		↓ bitter					⇓		
Foscarnet sodium	PDR (Foscavir)	Taste perversion										
Idoxuridine	Simpson, 1975	Unpleasant taste										
Interferon alfa-n3	PDR (Alferon)	Strange taste in mouth										
Interferon beta-1b	PDR (Betaseron)	Taste loss; taste perversion										
Rimantadine HCl	PDR (Flumadine)	Taste loss/change										
Agents for dental hygiene												
Sodium fluoride	Thumfart *et al.*, 1980	Loss of taste										

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Sodium lauryl sulfate	1. Rollin, 1978 2. De-Simone *et al.*, 1980	1. Hypogeusia or ageusia with occasional phantogeusia 2. Hypogeusia, dysgeusia										
Chlorhexidine digluconate mouthrinses	1. Lang *et al.*, 1988 2. PDR (Peridex)	1. Short-lasting taste impairment for salty taste 2. Alteration of taste perception										
Bronchodilators and antiasthmatic drugs												
Albuterol sulfate	PDR (Ventolin, Volmax, Proventil)	Unusual taste										
Beclomethasone dipropionate	1. Griffin, 1992 2. PDR (Beconase)	1. Taste loss, taste perversion 2. Loss of taste										
Bitolterol mesylate	PDR (Tornalate)	Unusual taste										
Cromolyn sodium	PDR (Gastrocrom, Intal, Nasalcrom)	Bitter aftertaste, taste perversion, bad taste										

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Ephedrine HCl + phenobarbitol + potassium iodide + theophylline calcium salicylate	PDR (Quadrinal)	Unpleasant brassy taste										
Flunisolide	PDR (AeroBid, AeroBid-M, Nasalide)	Unpleasant taste, loss of taste										
Metaproterenol sulfate	PDR (Metaproterenol Arm-a-Med, Alupent, Metaprel)	Bad taste										
Nedocromil	PDR (Tilade)	Unpleasant taste										
Pirbuterol acetate inhalation aerosol	PDR (Maxair autohaler & inhaler)	Taste changes										
Terbutaline sulfate	PDR (Brethaire)	Unusual taste										
Diuretics, antiarrhythmic, antihypertensive, and antifibrillatory agents												
Acetazolamide	1. Dahl *et al.*, 1984 2. PDR (Diamox, Diamox Sequels)	1. Decreased NaCl threshold 2. Taste alteration										

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Adenosine	PDR (Adenocard)	Metallic taste										
Amiloride and its analogs	PDR (Moduretic)	Bad taste	Bitter	⇓			⇓					
Amiodarone HCl	PDR (Cordarone)	Abnormal taste										
Amlodipine besylate	PDR (Norvasc)	Taste perversion										
Benazepril HCl & hydro-chlorothiazide	PDR (Lotensin HCT)	Taste perversion										
Betaxolol HCl	PDR (Kerlone)	Abnormal taste, taste loss										
Bisoprolol fumarate & bisoprolol fumarate with hydrochlorothiazide	PDR (Zebeta, Ziac)	Taste abnormalities										

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Captopril & Captopril/hydro-chlorothiazide	1. McFate Smith *et al.*, 1984 2. McNeil *et al.*, 1979 3. Vlasses & Ferguson, 1979 4. Griffin, 1992 5. PDR (Capoten, Capozide)	1. Taste disturbance 2. Dysgeusia 3. Ageusia 4. Taste loss, taste abnormal, taste perversion 5. Diminution or loss in taste perception, dysgeusia	0.132 ± 0.150 mM (Sour, bitter)		↓		↓					
Clonidine	PDR (Catapres-TTS)	Change in taste										
Diazoxide	1. Schiffman, 1983 2. PDR (Hyperstat IV)	1. — 2. Alteration of taste										
Diltiazem	1. Berman, 1985 2. PDR (Cardizem, Cardizem CD & SR)	1. Hypogeusia, possible dysgeusia 2. Dysgeusia	0.142 ± 0.03 mM (Bitter)			⇑ burn	⇑		⇑		⇓	
Doxazosin mesylate	PDR (Cardura)	Taste perversion										

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
1. Enalapril 2. Enalapril maleate 3. Enalaprilat	1a. McFate-Smith *et al.*, 1984 1b. Griffin, 1992 2,3. PDR (Vasotec, Vaseretic, Vasotec IV)	1a. Taste disturbance (loss & alteration) 1b. Taste loss, taste abnormal, taste perversion 2,3. Taste alteration	0.107 ± 0.03 mM (sour)						⇓			
Esmolol	PDR (Brevibloc)	Taste perversion										
Ethacrynic acid	Gifford, 1970	Metallic taste	0.1859 ± 0.056 mM (Bitter)						⇑			⇑
Flecainide acetate	PDR (Tambocor)	Change in taste										
Fosinopril sodium	PDR (Monopril)	Taste disturbance										
Guanfacine HCl	PDR (Tenex)	1a. Taste perversion, alterations in taste										
Hydro-chlorothiazide	Griffin, 1992	Taste loss, taste abnormal, taste perversion	n/a			⇑ bitter	⇓					⇓

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Labetalol HCl	PDR (Trandate, Normodyne)	Taste distortion	0.182 ± 0.04 mM (Bitter)			↓		↓		⇑		
Metolazone	PDR (Mykrox)	Bitter taste										
Mexiletine HCl	PDR (Mexitil)	Altered taste	0.463 ± 0.34 mM (Bitter)	⇓		↓	↓	↓		⇓	⇑	⇓
Moricizine HCl	PDR (Ethmozine)	Bitter taste										
Nifedipine	1. Levinson & Kennedy, 1985 2. PDR (Procardia XL)	1. Dysgeusia 2. Taste perversion	n/a									
Procainamide HCl	PDR (Procan SR)	Bitter taste	0.438 ± 0.10 mM (Bitter)		↓	↓				⇑		
Propafenone HCl	PDR (Rythmol)	Unusual taste	0.048 ± 0.03 mM (Bitter)		⇓			⇓	⇓			
Propranolol	Griffin, 1992	Taste loss, taste abnormal, taste perversion	0.209 ± 0.07 mM (Bitter)							⇑		

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Ramipril	PDR (Altace)	Taste disturbance										
Spironolactone	Griffin, 1992	Taste loss										
Tocainide HCl	PDR (Tonocard)	Taste perversion										
Triamterene/ Hydrochlorothiazide	PDR (Maxzide)	Taste alteration										
Hyper- & hypoglycemic drugs												
Diazoxide	PDR (Proglycem)	Transient loss of taste										
Glipizide	Lahon & Mann, 1973	Taste change										
Phenformin and derivatives	1. Rollin, 1978 2. Ferguson *et al.*, 1961	1. Metallic phantogeusia 2. Dysgeusia										
Hypnotics & sedatives												
Estazolam	PDR (ProSom)	Perverse taste										
Flurazepam HCl	1. Griffin, 1992 2. PDR (Dalmane)	1. Taste abnormal, taste perversion 2. Bitter taste										

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Midazolam HCl	PDR (Versed)	Acid taste										
Prochlorperazine			0.103 ± 0.045 mM (Bitter)						⇑			
Promethazine			0.079 ± 0.025 mM (Bitter)	⇓	↓	⇓	⇓		⇑ bitter			
Quazepam	PDR (Doral)	Abnormal taste perception										
Triazolam	1. Griffin, 1992 2. PDR (Halcion)	1. Taste loss, taste abnormal, taste perversion 2. Taste alterations										
Zolpidem tartrate	PDR (Ambien)	Taste perversion										
Zoplicone	Griffin, 1992	Taste loss, taste abnormal, taste perversion, taste altered										

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Muscle relaxants and drugs for treatment of Parkinson's disease												
Baclofen	1. Rollin, 1978 2. PDR (Lioresal, Lioresal Intrathecal)	1. Hypogeusia, ageusia with occasional phantogeusia 2. Taste disorder, decreased taste	3.50 ± 0.723 mM (Bitter-metallic)								↓	
Chlormezanone	Rollin, 1978	Hypogeusia or ageusia with occasional phantogeusia										
Cyclobenzaprine HCl	PDR (Flexeril)	Ageusia, unpleasant taste	0.349 ± 0.156 mM (Bitter)	⇓	⇓	⇓	⇓			⇑		
Dantrolene sodium	PDR (Dantrium)	Alteration of taste										
Levodopa	1. Siegfried & Zumstein, 1971 2. PDR (Dopar, Larodopa)	1. Ageusia followed by dysgeusia 2. Bitter taste										
Methocarbamol	PDR (Robaxin)	Metallic taste										

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Pergolide mesylate	PDR (Permax)	Taste perversion										
Selegiline HCl	PDR (Eldepryl)	Taste disturbance										
Psychopharmacologic including antiepileptic												
Alprazolam	PDR (Xanax)	Taste alterations										
Amitriptyline HCl	PDR (Elavil, Endep)	Ageusia, peculiar taste	0.155 ± 0.042 mM (Bitter)	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	
Amoxapine	PDR (Asendin)	Peculiar taste										
Buspirone HCl	PDR (BuSpar)	Altered taste	0.269 ± 0.147 mM (Bitter)			↑ bitter	↓	⇓		⇑		
Carbamazepine	Halbreich, 1974	Higher thresholds, altered taste										
Chlordiazepoxide & Amitriptyline HCl	PDR (Limbitrol)	Peculiar taste										
Clomipramine HCl	PDR (Anafranil)	Taste loss, taste perversion	0.122 ± 0.028 mM (Bitter)	⇓	⇓	⇓	⇓	⇓		↓		

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Clozapine	PDR (Clozaril)	Bitter taste										
Desipramine HCl	PDR (Norpramin)	Peculiar taste	0.161 ± 0.049 mM (Bitter)	↓					⇓	⇓	⇓	⇑
Doxepin HCl	PDR (Adapin, Sinequan)	Taste disturbances	0.143 ± 0.021 mM (Bitter)	⇓	⇓	⇓	⇓	⇓	⇓	⇓	↓	⇑
Felbamate	PDR (Felbatol)	Taste perversion										
Fluoxetine HCl	PDR (Prozac)	1. Taste change, taste perversion										
Imipramine HCl & imipramine pamoate	PDR (Tofranil)	Peculiar taste	0.125 ± 0.024 mM (Bitter)	⇓	⇓	⇓	↓	↓	⇓	↓	⇓	
Lithium carbonate	1. Bressler, 1980 2. Duffield, 1973 3. PDR (Eskalith, Lithium Carbonate, Lithionate/ Lithotabs)	1. Ageusic for NaCl 2. Strange, unpleasant taste associated with food 3. Metallic and salty taste, dysgeusia/ taste distortion										

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Maprotiline HCl	PDR (Ludiomil)	Bitter taste										
Nortriptyline HCl	PDR (Pamelor)	Peculiar taste										
Paroxetine HCl	PDR (Paxil)	Taste perversion										
Perphenazine-amitriptyline HCl	PDR (Triavil, Etrafon)	Bitter-tasting (perphenizine), peculiar taste (amitriptyline HCl)										
Phenytoin	Schiffman, 1983	—	n/a								⇑	
Pimozide	PDR (Orap)	Taste change										
Protriptyline HCl	PDR (Vivactil)	Peculiar taste										
Psilocybin	Fischer *et al.*, 1965	Lower jnd's for Na saccharin										
Risperidone	PDR (Risperdal)	Bitter taste										
Sertraline HCl	PDR (Zoloft)	Taste perversion										
Trazodone HCl	PDR (Desyrel)	Bad taste in mouth										
Trifluoperazine	Fischer *et al.*, 1965	Larger difference thresholds for Na saccharin	0.065 ± 0.012 mM (Bitter)	⇓	⇓	⇓		↓	⇓			⇑

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Trimipramine maleate	PDR (Surmontil)	Peculiar taste										
Venlafaxine HCl	PDR (Effexor)	Taste perversion										
Sympathomimetic drugs												
Amphetamine	1. Mata, 1963 2. PDR (Biphetamine)	1. Increased sensitivity to bitter taste & decreased sensitivity to sweet taste 2. Unpleasant taste										
Benzphetamine HCl	PDR (Didrex)	Unpleasant taste										
Dextroamphetamine-sulfate	PDR (Dexedrine)	Unpleasant taste										
Fenfluramine HCl	PDR (Pondimin)	Bad taste										
Mazindol	PDR (Sanorex)	Unpleasant taste										
Methamphetamine HCl	PDR (Desoxyn)	Unpleasant taste										

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Phendimetrazine tartrate	PDR (Prelu-2)	Bitter taste, unpleasant taste										
Phentermine resin, Phentermine HCl	PDR (Ionamin, Adipex-P, Fastin)	Unpleasant taste										
Vasodilators												
Bamifylline HCl	Rollin, 1978	Bitter phantogeusia										
Dipyridamole	Goy *et al.*, 1985	Dysgeusia										
Isosorbide mononitrate	PDR (Monoket)	Bitter taste										
Nitroglycerin patch	Ewing *et al.*, 1989	Ageusia										
Oxyfedrine	1. Rabe, 1970 2. Whittington & Raftery, 1980	1. Ageusia 2. Ageusia										
Others (indication)												
Allopurinol (reduces serum & urinary uric acid)	1. Rollin, 1978 2. PDR (Zyloprim)	1. Metallic phantogeusia 2. Taste loss/ perversion	n/a									

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Antihemophilic factor (recombinant) (clotting factor-hemophilia)	PDR (Kogenate)	Unusual taste in mouth										
Antithrombin III (human) (antithrombin III deficiency)	PDR (Thrombate III)	Foul taste in mouth										
Bepridil HCl (antianginal/ antispasmodic)	PDR (Vascor)	Taste change										
Calcitonin (Paget's Disease, hypercalcemia, osteoporosis)	PDR (Miacalcin, Cibacalcin)	Salty taste										
Etidronate (hypercalcemia, antipsoriatic)	1. Jones *et al.*, 1975 2. PDR (Didronel)	1. Transient taste loss 2. Metallic or altered taste; loss of taste (usually transient)										
Etretinate (antipsoriatic)	PDR (Tegison)	Taste perversion										

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Gadodiamide (diagnostic imaging product)	PDR (Omni-scan)	Taste perversion										
Germine monoacetate (Eaton-Lambert Syndrome)	Cherington, 1976	Unpleasant taste										
Granisetron HCl (antiemetic/ antinauseant)	PDR (Kytril)	Taste disorder										
Histamine phosphate (control for allergic skin testing)	PDR (Histatrol)	Metallic taste										
Iohexol (diagnostic imaging product)	PDR (Omnipaque)	Taste perversion										
Iron sorbitex (hematinic)	McCurdy, 1964	Metallic taste										
Leuprolide acetate (inhibits gonadotropin secretion/ prostatic cancer)	PDR (Lupron, Lupron Depot)	Taste disorders										

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Mesna (detoxifying agent)	PDR (Mesnex)	Bad taste in mouth										
Methazolamide (carbonic anhydrase inhibitor)	PDR (Neptazane)	Taste alteration										
Methylergonovine maleate (prevents post-partum hemorrhage)	PDR (Methergine)	Foul taste										
Nicotine (smoking cessation)	PDR (Nicoderm, Nicotrol)	Taste perversion										
Nicotine polacrilex (smoking cessation)	PDR (Nicorette)	Taste perception changes										
Pentoxifylline (blood viscosity modulator)	PDR (Trental)	Bad taste	0.930 ± 0.261 mM (bitter)	⇑		⇓						
Potassium iodide (expectorant)	PDR (Pima, SSKI)	Metallic taste										

TABLE XIII *(continued)*

DRUGS THAT INTERFERE WITH THE TASTE SYSTEM

Classification/ drug	Source	Taste complaint or description	Threshold	Effect of topical application on intensity or major taste quality								
				NaCl	KCl	$CaCl_2$	Sucrose	QHCl	Citric Acid	Capsaicin	WS-3	$FeSO_4$
Sermorelin acetate (diagnostic)	PDR (Geref)	Strange taste in mouth										
Succimer (lead poisoning)	PDR (Chemet)	Drug has unpleasant mercaptan odor/taste, metallic taste										
Terbinafine	Griffin, 1992	Taste loss, taste altered										
Ursodiol (gall stone dissolution)	PDR (Actigall)	Bitter-tasting, metallic taste										
Vitamin D/ Calcitriol (hypocalcemia)	1. Rollin, 1978 2. Schiffman, 1983 3. PDR (Calcijex, Rocaltrol)	1. Metallic phantogeusia 2. — 3. Metallic taste										
Vitamin K_1/ Phytonadione (coagulation disorders)	PDR (Aqua-mephyton & Mephyton)	Peculiar sensations of taste										

↑↓ refers to changes of less than 20%, ⇑⇓ to changes greater than 20%

Sources: Schiffman *et al.*, 1983, 1999a,b,c; Zervakis *et al.*; 2000; Schiffman *et al.*, 2000a,b

The first two columns of Table XIII give the generic and trade names of medications that have been associated clinically with taste disorders. The third column lists the clinical taste complaint with the reference given in column 2. The taste thresholds for 62 of the drugs as determined by Schiffman and colleagues are given in column 4. Column 4 also lists the most salient taste of the drug perceived by the subjects at four times higher than their detection thresholds. The detection thresholds given in column 4 are for young subjects; thresholds for elderly subjects were higher on average than those for younger subjects. The symbol "n/a" in the threshold column indicates that the drug either had no taste or was so insoluble in water that the threshold could not be determined. The next columns (5 through 13) indicate changes in intensity of taste qualities for other taste compounds when the tongue was treated with a drug. A single arrow indicates that the change in intensity was less than 20% while a double arrow indicates that the change was greater than 20%.

The results of this series of experiments with 62 drugs showed that taste detection thresholds ranged from as low as 2.9 μM for saquinavir (Invirase) to as high as 24 mM for didanosine. All of the drugs that induced a taste were bitter, sour, or metallic at a concentration 4 times the detection threshold. Furthermore, most of the drugs modified the taste of other compounds to different degrees. This nonhomogenous alteration of other tastes by drugs is likely responsible, in part, for the dysgeusia that is often experienced by elderly who are taking medications.

There are fewer drugs specifically implicated in smell disorders than for taste. This is shown in Table XIV which gives the generic and brand names for medications in columns 1 and 2 that have been associated with smell changes in clinical and experimental studies. Column 3 gives the type of study performed. Column 4 gives the odor impairment or change.

Medications may also induce taste problems secondarily by causing other types of oral side-effects. Dry mouth (xerostomia), an oral side effect of 80.5% of the 131 most frequently prescribed drugs for 1992, can impair oral health and potentiate taste disorders (Smith and Burtner, 1994). This is illustrated by the comparison of terfenadine (Seldane) and terfenadine/pseudoephedrine (Seldane-D). The frequency of xerostomia for terfenadine alone is 2.3–4.8% (Smith and Burtner, 1994) while the frequency of xerostomia for terfenadine/pseudoephedrine is 21.7%. Terfenadine alone is not associated with taste disorders while terfenadine/pseudoephedrine is reported to alter taste perception. The percent of elderly suffering from mouth dryness ranges from 20–40% (Rhodus and Brown, 1990; Gilbert *et al.*, 1993). Approximately half of the institutionalized elderly receive one or more drugs with a hyposalivary side effect such as antidepressants, antihistamines, and analgesics (Handelman *et al.*, 1986).

TABLE XIV

DRUGS THAT INTERFERE WITH THE SMELL SYSTEM

Classification/drug	Source	Type of study	Problem
AIDS-related therapeutic Drugs			
Zalcitabine	PDR (Hivid)	Clinical trial	Smell dysfunction, parosmia
Analgesic			
Sumatriptan succinate	PDR (Imitrex)	Clinical report	Disturbance of smell
Anesthetics, local			
Cocaine HCl and tetracaine HCl	Zilstorff, 1965	Experiment	Reduced smell sensation up to 2 hours
Anticholesteremic			
Probucol	PDR (Lorelco)	—	Diminished sense of smell
Antihypertensive and antiarrhythmic agents			
Amiodarone HCl	PDR (Cordarone)	Retrospective study	Abnormal smell
Diltiazem	Berman, 1985	Clinical	Anosmia; dysosmia
1a. Enalapril maleate 1b. Enalaprilat 1c. Enalapril maleate	PDR 1a. (Vaseretic) 1b. (Vasotec IV) 1c. (Vasotec)	1a. Clinical trial 1b. Clinical trial 1c. Clinical trial	1a-1c. Anosmia

TABLE XIV *(continued)*
DRUGS THAT INTERFERE WITH THE SMELL SYSTEM

Classification/drug	Source	Type of study	Problem
Nifedipine	Levinson & Kennedy, 1985	Clinical	Dysosmia
Propafenone HCl	PDR (Rythmol)	Clinical trial or report	Unusual smell sensation
Tocainide HCl	PDR (Tonocard)	Clinical trial	Smell perversion
Anti-inflammatory			
Beclomethasone dipropionate	PDR (Beconase)	Clinical trial	Loss of smell
Dexamethasone sodium phosphate	PDR (Decadron Turbinaire)	Clinical report	Anosmia
Flunisolide	PDR 1. AeroBid/AeroBid-M 2. Nasalide	1. Clinical trial 2. Clinical report	1. Loss of smell 2. Loss of smell
Flurbiprofen	PDR (Ansaid)	Clinical trial	Parosmia
Antimicrobial agents			
Allicin	Body, 1986	Comment	Onion/garlic odor
Ciprofloxacin	PDR (Cipro, Cipro IV, Cipro IV Pharmacy Bulk)	Clinical report	Anosmia

TABLE XIV *(continued)*
DRUGS THAT INTERFERE WITH THE SMELL SYSTEM

Classification/drug	Source	Type of study	Problem
Ofloxacin	PDR (Floxin)	Clinical report	Disturbance of smell
Pentamidine isethionate	PDR (NebuPent)	Clinical trial	Loss of smell
Streptomycin	Zilstorff & Herbild, 1979	Comment	Parosmia
Ticarcillin disodium and clavulanate potassium	PDR (Timentin)	Clinical report	Disturbance of smell
Tyrothricin	Seydell & McKnight, 1948	Clinical	Anosmia & odor perversions
Antithyroid agents			
Carbimazole	Erikssen *et al.*, 1975	Clinical	Anosmia
Methimazole	Hallman & Hurst, 1953	Clinical	Anosmia
Methylthiouracil	Schneeberg, 1952	Clinical	Hyposmia
Propylthiouracil	Grossman, 1953	Clinical	Anosmia
Bronchodilators and antiasthmatic drugs			
Bitolterol mesylate	PDR (Tornalate)	—	Unusual smell
Pirbuterol acetate inhalation aerosol	PDR (Maxair autohaler & inhaler)	Clinical trial	Smell changes

TABLE XIV *(continued)*
DRUGS THAT INTERFERE WITH THE SMELL SYSTEM

Classification/drug	Source	Type of study	Problem
Opiates			
Codeine	Macht & Macht, 1940	Experiment	Reduced odor sensitivity
Hydromorphone HCl	Macht & Macht, 1940	Experiment	Reduced odor sensitivity
Morphine	Macht & Macht, 1940	Experiment	Reduced odor sensitivity
Psychopharmacologic drugs			
Amitriptyline	1. Farbman *et al.*, 1988 2. Chuah & Hui, 1986	1. Experiment 2. Experiment	1. Affects neurite out-growth & reduces olfactory marker protein 2. Modification of olfactory bulb
Buspirone HCl	PDR (BuSpar)	Clinical report	Altered smell
Clomipramine HCl	PDR (Anafranil)	Clinical report	Parosmia
Radiation therapy			
Radiation to head	Carmichael *et al.*, 1984	Clinical	Anosmia
Sympathomimetic drugs			
Amphetamines	1. Goetzl & Stone, 1948 2. Schiffman, 1983 3. Turner, 1965	1. Experiment 2. Clinical 3. Experiment	1. Variable 2. Increase in acuity 3. Increase in acuity (fall in threshold)

TABLE XIV *(continued)*
DRUGS THAT INTERFERE WITH THE SMELL SYSTEM

Classification/drug	Source	Type of study	Problem
Phenmetrazine theoclate with fenbutrazate HCl	Turner, 1965	Experiment	Increase in acuity (fall in threshold)
Other (indication)			
Acetylcholine-like substances (cholinergic)	Skouby & Zilstorff-Pedersen, 1954	Experiment	Decreases smell threshold
Levamisole HCl (immunomodulator – restores depressed immune function)	PDR (Ergamisol)	Clinical trial	Altered sense of smell
Strychnine (central stimulant)	Skouby & Zilstorff-Pedersen, 1954	Experiment	Decreases smell threshold

Hyposalivation may concentrate some drugs into the saliva. Stimulated whole salivary flow rate (SWSFR) is reduced in elderly subjects who use xerostomia-inducing medications. In one study SWSFR was 0.94 ml/min for elderly subjects using xerostomia-inducing medications versus 1.52 ml/min for control subjects (Persson *et al.*, 1991). However, sensations of dry mouth can occur without abnormal salivary gland dysfunction.

The unpleasant tastes of medications can also induce physiological responses indicative of stress. Schiffman and colleagues (2000a) measured concentrations of plasma catecholamines and cortisol before and after oral exposure to 10 ml each of four taste stimuli presented sequentially in a fixed order: water (control), carbonated water, Invirase (a bitter drug), and capsaicin (component in chili pepper). Invirase (0.09 mM) and capsaicin (100 ppm) had strong perceived intensities but were not harmful to the subjects. None of the stimuli were swallowed. Blood samples were taken just prior to the delivery of each of the four taste stimuli and at 5 minutes, 10 minutes, and 25 minutes after each stimulus administration. There was a 25 minute interval between each test stimulus. The main finding was that plasma levels of norepinephrine increased significantly after a single presentation of the bitter-tasting drug Invirase and did not return to baseline after the 25 minute rest period (see Figure 1). The oral irritant (capsaicin) also elevated plasma norepinephrine levels. Neither epinephrine nor cortisol, however, were altered by a single presentation of these stimuli. These findings are consistent with previous research that has found increases in norepinephrine (fight hormone which provides drive to meet the challenge with action) in the early stages of arousal and stress. More intense and sustained exposure to bitter or irritating drugs may affect elevate epinephrine (fight/flight, anxiety) or ultimately cortisol (helplessness, depression) (see Henry, 1993, 1997). Increase in stress hormones may be due to evolutionary association of bitter taste with poisons.

VI. FLAVOR ENHANCEMENT COMPENSATES FOR TASTE AND SMELL LOSSES IN ELDERLY PERSONS

Numerous studies have found that flavor enhancement of table foods and liquids with simulated food flavors can compensate for taste and smell losses and improve immune status. Simulated flavors consist of mixtures of odorants (i.e. odorous molecules) that are extracted or blended from natural products; alternatively they can be synthesized in the laboratory based on chromatographic and mass spectrographic analysis of natural products. Some flavors also contain nonvolatile compounds such as amino acid salts (e.g. monosodium glutamate) that induce taste stimulation.

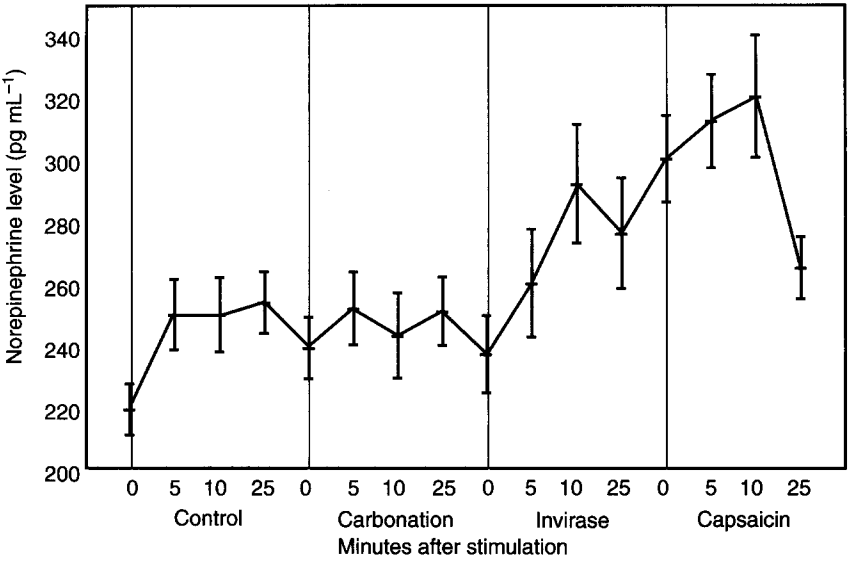

FIG. 1. Norepinephrine values at baseline and 5, 10, and 25 minutes after four stimuli: (a) control (water), (b) carbonation, (c) Invirase, and (d) capsaicin.

Flavor enhancement differs from conventional cooking techniques for increasing flavor with spices, herbs, and salt. Spices and herbs impart different flavors to the food rather than intensify actual food flavors. Five studies are described below that have utilized flavor enhancement of foods for the elderly to improve food palatability and acceptance, improve lymphocyte counts, increase salivary flow, and/or increase secretion rate of salivary immunoglobulin A (sIgA).

A. STUDY 1: FLAVOR ENHANCEMENT INCREASES LYMPHOCYTE COUNTS IN ELDERLY RETIREMENT HOME RESIDENTS

Schiffman and Warwick (1993) found that flavor enhancement of several food items at a meal for elderly retirement home residents resulted in improved immune status as determined by T and B lymphocyte levels and improved grip strength. Thirty-nine elderly independent living residents at a retirement home (mean age 84.6 years) participated in the study. A three-week meal plan was developed, and the subjects were divided into two groups. Group 1 was served foods that were unenhanced by flavor for the first three weeks; they were served the same foods enhanced with flavor for the second three-week period. For group 2, the order was

reversed; they received enhanced foods for the first three-week period and unenhanced foods for the second three-week period. The menu plan during the three weeks of flavor enhancement was identical to the menu plan during the unenhanced three-week period. Flavors were added to some but not all foods at a meal in the flavor enhanced condition.

The six flavors added to foods throughout the study were the following: roast beef, ham, natural bacon, prime beef, maple, and cheese. The flavors contained odorous compounds but no taste compounds such as monosodium glutamate, NaCl, or sweeteners. The flavors were added to vegetables (cauliflower, succotash, cabbage, peas, French cut green beans, mustard greens, Normandy vegetables, parsley cauliflower, peas and carrots, kale, spinach, stewed tomatoes, waxed beans, yellow squash, zucchini squash), gravies and sauces (mushroom gravy, prime beef brown gravy, roast beef brown gravy, roast pork gravy, Spanish sauce, tomato gravy, tomato sauce, vegetable gravy), breakfast foods (eggs, grits, maple syrup, oatmeal), and other main courses (soups, stews, and macaroni and cheese). These 30 foods were selected because they were nutrient dense. For example, simulated beef flavor was added to beef or beef stock to provide a more intense "beef" sensation. The flavor levels were similar to those of concentrated orange juice or extract of vanilla.

Biochemical, anthropometric, and functional measures were taken at the beginning of the study, at the end of three weeks, and at the end of six weeks for every subject. Food consumption was measured for every meal for five days of the week. The main findings were the following. First, addition of flavors increased mean intake for 20 out of 30 foods. However, the increased consumption did not shift the overall caloric intake or dietary nutrient profile. Analysis of the data revealed that subjects consumed the same macro- and micronutrients on the two arms of the study. This occurred because some but not all foods at a meal were enhanced during the three-week flavor-enhancement period; subjects simply ate more enhanced food and less unenhanced food. The second main finding was that immune function was improved (as determined by elevated T and B lymphocyte counts) after consumption of the flavor-enhanced food for three weeks, and this improvement was not attributable to altered intake of macro- and micronutrients. The third finding was that grip strength in both hands was improved after consumption of flavor-enhanced foods for three weeks.

This study was replicated using four-week (rather than three-week) food plans in which monosodium glutamate (to intensify taste) as well as flavors were added on the flavor enhanced arm of the study. Monosodium glutamate (MSG) has a meaty taste quality that is called "umami" in the Japanese language. The concentration of sodium in MSG required to

optimize the taste preferences is much lower than that required for NaCl. The findings of this study that used MSG in conjunction with flavors yielded similar results as the previous one (Schiffman, 1998).

The increases in T and B cell counts obtained from eating flavor-enhanced food are important because they provide a mechanism to counteract the progressive immunological decline that occurs with age. Reduced effectiveness of the T cell-dependent immune system in the elderly due in part to thymic involution in immune responsiveness is one reason for the increased susceptibility to infections found in older individuals.

B. STUDY 2: TASTE AND ODOR STIMULATION INCREASES SALIVARY FLOW AND IMPROVES SECRETION RATE OF SALIVARY IGA

Schiffman and Miletic (1999) reported two experiments in which taste and odor stimuli increased the secretion rate of salivary IgA (sIgA). Both young (mean age = 32.4 years) and elderly (mean age = 73.2 years) individuals participated in the experiments. In the first experiment, three different types of drops were delivered to the tongue: (1) "flavor" drops (5% cocoa powder, 60% sugar, and 0.1% Irish cream odor); (2) sugar (60%) (sugar control); and (3) water (water control). The drops were administered three times in 1 gram drops over a one-hour period: at $t = 0$, at $t = 30$ minutes, and at $t = 60$ minutes. In the second experiment, two solid foods (corn, carrots) and two soups (chicken broth, and onion soup) were tested with and without monosodium glutamate. Each food or soup was consumed three times in 6.5 gram samples over a one hour period: at $t = 0$, at $t = 30$ minutes, at $t = 60$ minutes.

In both of the experiments, salivary samples were collected four times: (1) prior to chemosensory stimulation (baseline), (2) immediately following chemosensory stimulation at $t = 0$ minutes, (3) immediately following chemosensory stimulation at $t = 30$ minutes, and (4) immediately following chemosensory stimulation at $t = 60$ minutes. The method for collecting saliva was a standardized method described by Miletic *et al.* (1996). Concentrations of IgA in the saliva were measured using capture ELISA and radial immune diffusion.

In the first experiment, application of sugar (taste alone) and flavor (taste and odor combined) to the tongue induced significantly higher secretion rates of sIgA than the water control for both young and elderly subjects. Furthermore, flavor application (in combination with sugar) produced significantly higher absolute concentrations of sIgA than sugar alone. Secretion rates of sIgA were significantly higher in young persons than those in elderly persons.

In the second experiment, the increase in the secretion rate of sIgA for the elderly subjects at 30 minutes and 60 minutes for each food containing

MSG was greater than that for the same food without MSG. It was concluded that chemosensory stimulation increases secretion rates of sIgA by increasing saliva production (both experiments). Furthermore, adding odor to the sugar drop (in the first experiment) increased the absolute concentration of sIgA perhaps through neural-immune connections. The increases in sIgA secretion rates found in these two experiments have important implications for elderly who suffer from dry mouth/reduced salivary flow (and hence reduced oral mucosal immunity) due to medications they are taking.

C. STUDY 3: SENSORY ENHANCEMENT OF FOODS FOR SICK ELDERLY INCREASES INTAKE AND IMPROVES NUTRITIONAL PARAMETERS

Schiffman (1998) found that addition of a combination of flavors and MSG to foods improved intake in 43 hospitalized patients. Each patient had clinical manifestations of malnutrition, a recent weight loss of 6% or more, and/or was below ideal weight. For two days, all foods served to each patient were measured before and after eating; on one of the days the patient received foods with added flavors and MSG; on the other day the foods were unenhanced. The energy density and sodium levels (2400 mg) of the food served on the two days was identical. The concentrations of flavors and MSG added to the food were individualized based on psychophysical measurements of each patient's taste and odor thresholds. The main finding was that 40 of 43 patients consumed at least 10% more calories on the day they were served flavor-enhanced food than on the unenhanced day. Furthermore, sensory enhancement in a subset of patients followed for one week or more led to improved plasma protein levels (including somatomedin-C/insulin-like growth factor I, albumin, or transferrin) and T-lymphocytes for some patients.

D. STUDY 4: FLAVOR ENHANCEMENT OF THE ENTREE AT DINNER CAN REDUCE SODIUM LEVELS IN A MEAL BY 500 mg

Schiffman and Graham (2000) studied satisfaction ratings at six retirement communities for the dinner meal in which flavors were added to an unsalted entree to compensate for salt. Throughout the eight-week study, two entrees (chicken breast and beefsteak) were each served once a week. During the first two weeks (baseline), the entrees (beef or chicken) were salted with the preferred level of table salt for this population (at least 500 mg sodium). For the next six weeks, the entrees were marinated in sodium-free chicken or beef flavor prior to cooking. No table salt was

available for residents to add to the beef or chicken at the table. Two vegetables accompanied the entree, both of which were lightly salted. During the six weeks of flavor enhancement, the sodium content of the two test meals was reduced by 500 mg.

Residents rated their satisfaction with the sensory properties of the dinner meals at which chicken breast or beefsteak were served after completing the meal. The main finding was that there was no difference in the degree of satisfaction between the salted version of the entree (during the two week baseline) and the flavor-enhanced (sodium-free) version (during the six weeks of flavor enhancement). This finding suggests that amplification of odor can substitute for salt in a beef or chicken entree as long as two lightly salted vegetables accompany the meal. That is, addition of flavors to beef and chicken entrees can replace salt with no significant adverse effects on acceptability of flavor. Use of salt-free flavors could be especially helpful to patients with hypertension who wish to comply with a low-sodium diet.

E. STUDY 5: FLAVOR ENHANCEMENT INCREASES PREFERENCE FOR VEGETABLES AND OTHER FOODS

Altered chemosensory perception in cancer patients has been associated with inadequate food intake and/or weight loss (Williams and Cohen, 1978; Bolze *et al.*, 1982; DeWys and Walters, 1975; Ames *et al.*, 1993). Cancer patients who perceive food to be unpalatable or aversive may reduce the diversity of foods consumed and fail to eat enough to meet nutritional requirements (Nielsen *et al.*, 1980; Bernstein and Bernstein, 1981). The results of a recent study of flavor preferences in 13 cancer patients currently undergoing chemotherapy or radiotherapy for breast cancer (Schiffman and Graham, 2000) indicate that cancer patients, like elderly without cancer, preferred flavor-enhanced foods. Breast cancer patients were asked to taste, smell, and swallow two samples of a food (one flavor-enhanced and one without additional flavor) and indicate which one they preferred. In all cases, the flavor-enhanced food was significantly preferred to the unenhanced version. These data suggest that flavor amplification can potentially reduce complaints about sensory properties of foods.

VII. CONCLUSION

Altered taste and smell functioning is common in the elderly population. Taste and smell impairments are due to the process of aging, medication

use, diseases, and environmental exposure. These chemosensory losses not only reduce the pleasure and comfort from food but can contribute to malnutrition and weight loss. In addition, elderly persons with chemosensory losses are more vulnerable to food poisoning or overexposure to environmentally hazardous chemicals, which are otherwise detectable by taste and smell. Enhancing food flavors at a meal can compensate for smell and taste losses. Flavor enhancement has been shown to increase enjoyment of food and improve food intake and immune status.

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