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CLINICAL PHYSIOLOGY OF TASTE AND SMELL

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CONTENTS

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INTRODUCTION

A report to the National Advisory Neurological and Communicative Disorders and Stroke Council (198) estimates that a significant number of Americans (approximately 2,000,000 people) suffer from losses, diminution, or distortion of their senses of taste, smell, or both. Although these disorders are seldom life-threatening, they can influence the health and well-being of the person who suffers from them (229). Taste and smell not only play a role in protection against harmful substances but they also contribute significantly to nutritional status as well as to the quality of life.

The senses of taste and smell convey the attractive properties of foods that promote and maintain food intake. When chemosensory disorders diminish or distort these senses, the taste and smell of foods can become uninteresting or even repugnant, which may lead to reduced food intake and compromised nutritional status. Persons with reduced taste and smell sensitivity may overcompensate for losses by increasing intake of substances that can be harmful if ingested in excess. For example, the increased taste thresholds for sweet sensation that commonly accompany aging can lead elderly diabetic patients to ingest too much sugar (229). Age-related losses in NaCl perception can be harmful to persons with hypertension. Decrements in taste and smell may also expose patients to harmful substances such as environmental contaminants and spoiled food. Overall, chemosensory dysfunction can reduce quality and enjoyment of life, deprive the individual of protective mechanisms, and can even contribute to stress, depression, and anorexia.

CLASSIFICATION OF CHEMOSENSORY DISORDERS

Disorders of taste and smell can be classified into five broad categories, depending on the degree or type of symptoms (270). These disorders are diagnosed by psychophysical evaluation in which patients are tested with a variety of chemical compounds.

1. Ageusia: total loss of taste sensitivity to some or all stimulants (tastants).
2. Hypogeusia: decreased taste sensitivity to some or all stimulants (tastants).
3. Dysgeusia (parageusia): distortion of taste for some or all tastants, or the perception of taste in the absence of any tastants (gustatory hallucination).
4. Hypergeusia: increased taste sensitivity to some or all stimulants (tastants).
5. Taste agnosia: complete or partial inability to identify, classify, or contrast a tastant verbally despite ability to recognize and distinguish between tastants.

Smell disorders fall into five similar categories:

1. Anosmia: total loss of sensitivity to odors.
2. Hyposmia: decreased sensitivity to odors.
3. Dysosmia: distortion of smell for some or all odorants, or the perception of odor in the absence of any odorants (olfactory hallucination).
4. Hyperosmia: increased odor sensitivity to some or all stimulants (odorants).
5. Smell agnosia: complete or partial inability to identify, classify, or contrast an odorant verbally despite ability to recognize and distinguish between odorants.

ANATOMY AND PHYSIOLOGY OF TASTE AND SMELL

To gain an understanding of taste and smell disorders, it is helpful to be familiar with the anatomy and physiology of chemosensory systems (see 249 for a review).

Taste

The sensory organs that mediate the sense of taste are the taste buds. These pear-shaped organs are found on the tongue, soft palate, pharynx, larynx, epiglottis, uvula, the upper third of the esophagus, and (especially in infants) the lips and cheeks. Taste buds on the tongue are contained in small specialized structures called papillae. There are three types of papillae: fungiform, circumvallate, and foliate. Fungiform papillae are elevated structures located on the anterior two thirds of the tongue; each fungiform papilla contains an average of 1 to 18 taste buds, although many fungiform papillae contain no buds at all. Circumvallate papillae are large mushroom-shaped structures arranged in a V shape on the posterior tongue and are surrounded by a "moat." Foliate papillae are vertical folds on the lateral border of the tongue, just anterior to the circumvallate papillae. Taste buds consist of about 50 cells that have a life span of approximately 10 to 10 1 2 days. Taste cells are constantly replaced by division of epithelial cells that surround the bud.

Three cranial nerves transmit taste signals from taste buds. The taste buds on the fungiform papillae, the anterior foliate papillae, and most buds on the soft palate are innervated by the seventh cranial nerve. Buds on the circumvallate papillae and posterior foliate papillae are innervated by the ninth cranial nerve. Buds on the pharynx, larynx, epiglottis, and uvula are innervated by the tenth cranial nerve. Taste information is transmitted to the cortex (cortical taste area) via the nucleus of the solitary tract and thalamus. Some taste information is also transmitted to the hypothalamus, which is integral to the feeding system in the brain. The three cranial nerves also contain

some axons that terminate in the spinal trigeminal nucleus, and it is presumed that these fibers convey thermal and tactile information from the oral cavity.

The taste system is stimulated by a wide range of chemicals including organic and inorganic compounds. The range of taste sensations is broad and includes not only sweet, sour, salty, and bitter qualities but "umami" (glutamate), astringent, and other tastes that are difficult to describe in words.

Smell

The receptors for smell are located in the olfactory epithelium in the pigmented upper part of the superior turbinate, the nasal septum, and the roof in between these regions. These receptors are specialized bipolar neurons with cilia that protrude into the mucus that covers the olfactory epithelium. Like taste cells, the receptor portion of the bipolar olfactory cells is constantly renewed from basal cells, but the turnover time is three times longer, approximately 30 days (191).

The very thin axons of bipolar neurons are aggregated in bundles that traverse small holes in the cribriform plate to reach the olfactory bulb where they form small bushy masses called glomeruli. With age, the glomeruli deteriorate and assume a moth-eaten appearance as the fibers disappear. Projections from the olfactory bulb then project to the primitive cortex including the pyriform lobe and hippocampal formation. The areas of primitive cortex not only process olfactory information but also process emotional information. The neurons in the hippocampus and pyriform cortex degenerate with age sooner than other parts of the brain. Like the taste system, olfactory information also projects to the hypothalamic feeding centers.

TYPES OF CHEMOSENSORY LOSSES

While taste and smell disorders are associated with a wide variety of conditions (including drug therapy, disease states, normal aging, Alzheimer's disease, and pollution), they can generally be classified by three major types of losses: transport losses, sensory losses, and neural losses (268). The term *sensori-neural losses* is used in situations in which it is difficult in practice to distinguish between sensory and neural disorders.

Transport losses interfere with the access of a chemical stimulus to the taste or smell receptors. A common example in the case of smell is nasal airway blockage by swollen membranes or structural abnormalities such as polyps and a deviated septum. In taste, transport losses can result from blockage of taste buds by bacterial colonizations, xerostomia, inflammation of the oral cavity, or poor oral hygiene.

Sensory losses are caused by damage to the sensory organs themselves (229). Toxic chemicals, radiation therapy, medications, neoplasms, endocrine and viral infections that reduce cell turnover or directly modify cells, can

impair taste and smell functioning. For example, radiation treatment can reduce cell turnover and cause aberrations in the sense of taste. Medications with sulfhydryl groups in their molecular structure such as penicillamine (antirheumatic drug) and captopril (antihypertensive agent) probably cause taste disorders because they interfere with receptor proteins on the surface of taste cells.

Neural losses result from damage to either the peripheral neural pathways that mediate taste and smell information or to the central nervous system. Common causes include head trauma, neoplasms, and surgical procedures. For example, head trauma resulting from an automobile accident can sever the nerve pathways through the cribriform plate to produce olfactory dysfunction.

CLINICAL EVALUATION

The clinical evaluation of a patient who presents with symptoms of chemosensory dysfunction normally consists of four components: (*a*) a history, (*b*) a physical examination, (*c*) psychophysical testing, and (*d*) medical imaging (269). The general strategy is first to make an anatomic diagnosis and then to make an etiologic diagnosis.

Patient History

The first step in diagnosis is the patient history. The patient is asked to describe the events associated with the onset of a taste or smell disorder. Patients are encouraged to recall events that coincided with the time of onset of the symptoms such as viral infections and head injuries. They are given ample opportunity to describe their chemosensory symptoms in detail. It is important to determine the following points: (*a*) whether the onset of symptoms was sudden or gradual; (*b*) whether the sensory loss applies to selected stimuli or all stimuli; (*c*) whether the changes are qualitative or quantitative; (*d*) whether the loss is intermittent (temporary losses suggest a transport problem) or continuous; (*e*) whether the sense is lost, diminished, enhanced, or distorted; (*f*) whether other symptoms accompany the disorder such as nasal or oral dryness, excess salivation, burning tongue, dental pain, or headache; (*g*) whether the patient is taking medications; (*h*) whether the patient has medical problems that may cause a chemosensory disorder. The patient's history should include family medical history and patient's social and occupational history including occupational exposures, substance abuse, and dietary history.

Physical Examination

The second step in diagnosis is a complete examination of the head and neck, including ears and upper respiratory tract. A neurologic examination of the cranial nerves is also necessary.

The nasal airways are examined to identify any obstructions that may interfere with transport of olfactory stimuli to the receptors in the olfactory epithelium. After initial visual examination, a vasoconstrictor is applied to improve visualization. The nasal mucous membrane is examined for abnormal conditions including inflammation, swelling, erosion, ulceration, epithelial metaplasia, and purulent discharge. Examination of the olfactory neuroepithelium itself is difficult even with the smallest of modern instruments.

The mucous membranes of the oral cavity should be examined for inflammation, swelling, dryness, abnormal texture, exudate, edema, atrophy erosion, ulceration, leukoplakia, and erythroplasia. Changes in the fungiform or circumvallate papillae should be noted.

Psychophysical Testing

All patients who report chemosensory dysfunction should be subjected to psychophysical evaluation of both taste and smell. Subjects often confuse a smell disorder with a taste disorder. The reason for this is that food is placed in the oral cavity and hence the patient attributes losses to taste rather than smell. However, the flavor of food is based on combined responses of the taste buds, olfactory neurons, and free nerve endings in the nose, mouth, and throat. Odor from food placed in the oral cavity reaches the olfactory receptors via the nasal pharnyx. A variety of psychophysical tests at threshold concentrations and suprathreshold concentrations are described in later sections on chemosensory losses in aging and Alzheimer's disease.

Medical Imaging

Computed tomography of the head provides important diagnostic information, expecially for olfactory disorders, by providing details about the structure of the nasal cavities, the cribriform plates, and the anterior cranial fossa (150). The presence of sinusitis and neoplasms of the nose, paranasal sinuses, and cranial cavity are diagnosed with computed tomography techniques. Magnetic resonance imaging can also be helpful in evaluating the contents of the cranial cavity, but computed tomagraphy is superior in providing detail on the bony structures.

DYSFUNCTIONS RESULTING FROM DRUGS

Medications that have been reported to alter chemosensory functioning are given in Tables 1 and 2. The drugs that alter chemosensory functioning have been shown to produce their effects after oral administration, systemic injection, or direct application to the chemosensory receptors. However, our current understanding of the mechanisms by which these pharmaceutical

Table 1 Drugs that interfere with the taste system

Classification	References
Amebicides and antihelmintics	
Metronidazole	283
Niridazole	209
Anesthetics (local)	
Benzocaine	295
Procaine hydrochloride (novocain)	295
Lidocaine	306
Anticholesteremic	
Clofibrate	105
Anticoagulants	
Phenindione	253
Antihistamines	
Chlorpheniramine maleate	229
Antimicrobial agents	
Amphotericin B	216
Ampicillin	134
Bleomycin	273
Cefamandole	125
Griseofulvin	78
Ethambutol hydrochloride	216
Lincomycin	105
Sulfasalazine	216
Tetracyclines	168, 229 271
Antiproliferative, including immunosuppressive agents	
Doxorubicin and methotrexate	60, 96
Azathioprine	216
Carmustine	211
Vincristine sulfate	275
Antirheumatic, analgesic-antipyretic, antiinflammatory	
Allopurinol	216
Colchicine	15
Dexamethasone	72
Gold	216
Hydrocortisone	72
Levamisole	219
D-penicillamine	147, 277
Phenylbutazone	216
Salicylates	19, 102
Sodium fluoride	288
5-Thiopyridoxine	130
Antiseptics	
Hexetidine	208

Table 1 (*continued*)

Classification	References
Antithyroid agents	
Carbimazole	66
Methimazole	66, 98
Methylthiouracil	250
Propylthiouracil	94
Thiouracil	216
Agents for dental hygiene	
Sodium lauryl sulfate	216, 50
Chlorhexidine digluconate mouth rinses	157
Diuretics and antihypertensive agents	
Acetazolamide	45, 91
Amiloride and its analogs	177, 237, 241
Captopril	180, 181, 294
Diazoxide	229
Diltiazem	17
Enalapril	180
Ethacrynic acid	85
Nifedipine	162
Hypoglycemic drugs	
Glipizide	154
Phenformin and derivatives	74, 216
Muscle relaxants and drugs for treatment of Parkinson's disease	
Baclofen	216
Chlormezanone	216
Levodopa	261
Psychopharmacologic agents	
Carbamazepine	97
Lithium carbonate	23, 59
Phenytoin	229
Psilocybin	75, 76
Trifluoperazine	75, 76
Sympathomimetic drugs	
Amphetamines	176
Vasodilators	
Bamifylline hydrochloride	216
Dipyridamole	90
Nitroglycerin patch	69
Oxyfedrine	210, 303
Others	
Etidronate	139
Germine monoacetate	34
Idoxuridine	262
Iron sorbitex	179
Vitamin D	216, 229

Table 2 Drugs that intefere with the smell system

Classification	References
Anesthetics, local	
Cocaine hydrochloride and tetracaine hydrochloride	307
Antihypertensive drugs	
Diltiazem	17
Nifedipine	162
Antimicrobial agents	
Allicin	18
Streptomycin	308
Tyrothricin	258
Antithyroid agents	
Carbimazole	66
Methimazole	66, 98
Methylthiouracil	250
Propylthiouracil	94
Opiates	
Codeine	166
Hydromorphone hydrochloride	166
Morphine	166
Psychopharmacologic drugs	
Amitriptyline	35, 71
Radiation therapy	
Radiation to head	30
Sympathomimetic drugs	
Amphetamines	87, 229, 290
Phenmetrazine theoclate with fenbutrazate hydrochloride	290
Vasodilators	
Diltiazem	17
Other	
Acetylcholine-like substances	265
Strychnine	265

agents modify the taste and olfactory systems is limited, and there are several reasons for our lack of knowledge. First, most drugs that cause chemosensory dysfunctions affect only a small minority of patients. Thus, well-controlled clinical trials to establish the cause of a taste or smell dysfunction are impractical because they would require such a large number of subjects. Second, persons taking medications have concomitant diseases that may contribute to the chemosensory disorder. Third, the transduction mechanisms for taste and smell at the receptor level are not fully understood; thus it is premature in most cases to speculate on the mechanisms by which drugs alter chemosensory functioning. Fourth, the neurotransmitters responsible for relaying taste and olfactory information from the periphery to the brain are

not well documented. Hence, the interference with the transmission of neural signals by drugs is not well understood.

Many taste complaints resulting from medications are simply due to the taste of the drug itself rather than to some modification of the taste system. The drug may be administered in a dosage form that does not mask its unpleasant taste. The drug may also reach the taste receptors by excretion into the saliva or by an intravascular route (21). In order to determine if the taste of the drug itself is the source of the complaint, the drug can be dissolved in water (or alcohol and water if necessary to achieve solubility) to determine if the taste sensation matches the taste of the solution. Odor complaints are seldom due to the odor of a drug, but this can be determined by a simple sniff test.

Drugs may also produce pharmacologic changes in chemosensory systems. The mechanism by which the drug alters the taste or smell systems may be identical to or different from the mechanisms by which it produces its pharmacologic effect on other tissues. Numerous medications given in Tables 1 and 2 have been shown to affect turnover of cells in other biological systems and thus may also affect turnover of taste and olfactory cells by the same mechanism.

DYSFUNCTIONS ASSOCIATED WITH DISEASES

A broad range of medical conditions leads to losses in taste and smell (see Tables 3 and 4). These medical conditions can affect chemosensory functioning in a multitude of ways. First, decreased turnover of receptors may be the cause in many of these illnesses. Decreased turnover in the chemosensory systems would be consistent with decreased cell proliferation that has been found in small-bowel epithelium after fasting (including starvation and protein deprivation), uremia, ionizing irradiation, and administration of methotrexate. Endocrine factors, including adrenalectomy, hypophysectomy, thyroidectomy, and castration, also lead to reduced cell renewal in small-bowel epithelium (229). Decreased levels of vitamins and minerals such as niacin and zinc respectively may also contribute to reduced turnover in malnourished patients.

The most frequent causes of losses in olfaction are viral infections, normal aging, head injuries that sever neurons coursing through the cribriform plate, and local obstructions (229, 232). For taste, the most common offenders are viral infections, dental problems, and drugs, especially those containing sulfhydryl groups in their chemical structures (229). Some odorants can also cause pain by increasing nasal resistance and blood flow to the nasal cavity (54).

Table 3 Medical conditions that affect the sense of taste

Condition	Reference	Condition	Reference
Nervous			
Alzheimer's disease	233	Gonadal dysgenesis (Turner's syndrome)	103
Bell's palsy	62	Pseudohypoparathyroidism	104
Damage to chorda tympani	136	Local	
Guillain-Barre syndrome	274	Facial hypoplasia	108
Familial dysautonomia	110	Glossitis and other oral disorders	22, 137
Head trauma	223	Leprosy	272
Multiple sclerosis	31, 39	Oral Crohn's disease	80
Raeder's paratrigeminal syndrome	77	Radiation therapy	40, 143
Tumors and lesions	63, 197	Sjögren's syndrome	116
Nutritional		Cushing's syndrome	107
Cancer	52, 82	Cretinism	259
Chronic renal failure	37	Viral and infectious	
Liver disease including cirrhosis	28, 83, 267	Influenza-like infections	112
Niacin deficiency	92	Other	
Thermal burn	38	Amyloidosis and sarcoidosis	225, 291
Zinc deficiency	201	Cystic fibrosis	51, 113, 118
Endocrine		High altitude	146
Adrenal cortical insufficiency	107	Hypertension	70, 106, 293
Congenital adrenal hyperplasia	107	Laryngectomy	145
Panhypopituitarism	107	Psychiatric disorders	4
Hypothyroidism	178, 222		
Diabetes mellitus	99		

DYSFUNCTIONS ASSOCIATED WITH NORMAL AGING

A general decline in both taste and smell perception occurs during aging with losses at both threshold and suprathreshold levels. Both detection thresholds and recognition thresholds are elevated in elderly individuals. A detection threshold is the absolute threshold of sensation; it is the lowest concentration of a tastant or odorant at which it is first detected. A recognition threshold is the lowest concentration at which the stimulus is correctly identified. Taste and olfactory losses also occur at suprathreshold concentrations.

The age at which these losses occur is not well established because individual subjects have never been followed longitudinally to determine the rate or extent of loss over the life span. However, cross-sectional studies suggest that a systematic decrement in olfaction begins around sixty years of

Table 4 Medical conditions that affect the sense of smell

Condition	Reference	Condition	Reference
Nervous			
Alzheimer's disease	184, 233, 256, 257	Pseudohypoparathyroidism	104, 301
Down's syndrome	298	X-linked ichthyosis due to steroid sulfatase deficiency	6, 285
Epilepsy	44		
Head trauma	159, 161, 189, 223, 284	Local	
Korsakoff's syndrome	138, 170	Adenoid hypertrophy	84
Migraine	43, 305	Allergic rhinitis, atopy, and bronchial asthma	36, 73
Multiple sclerosis	207	Crouzon's syndrome	46
Parkinson's disease	7, 55, 297	Leprosy	14
Tumors and lesions	12, 81, 135, 203	Ozena	282
Nutritional & metabolic		Paranasal sinus exenteration	127
Chronic renal failure	244	Sinusitis and polyposis	73, 126, 221
Liver disease including cirrhosis	28, 83	Sjögren's syndrome	116
Trimethylaminuria	160	Viral and infectious	
Vitamin B_{12} deficiency	218	Acute viral hepatitis	115
Endocrine		HIV infection	26
Adrenal cortical insufficiency	107	Influenza-like infections	112
Cushing's syndrome	107	Other	
Hypothyroidism	178, 222	Amyloidosis and sarcoidosis	48, 225
Diabetes mellitus	140	Cystic fibrosis	113, 118
Gonadal dysgenesis (Turner's syndrome)	103	Familial (genetic)	264
Hypogonadotropic hypogonadism (Kallman's syndrome)	142, 171	Laryngectomy	109, 111
		Psychiatric disorders	182
Primary amenorrhea	175		

age and becomes significantly worse after seventy (57, 248). Taste losses may occur slightly later.

Taste: Threshold Losses

Increased taste thresholds in elderly persons have been reported for salty tastes (95, 192, 235, 300), sweet tastes (188, 192, 240), sour tastes (86, 192, 231), bitter tastes including phenythiourea-type compounds (41, 86, 144, 192, 236, 300), amino acids (238), glutamate salts (236), and weak galvanic currents (129).

An examination of recent threshold data (231) reveals that losses at threshold levels are not uniform across tastants. Average losses varied across different taste qualities. The average detection threshold in elderly individuals was 2.72 times higher than in young persons for sweeteners, 11.58 times higher for sodium salts, 4.29 times higher for acids, 6.94 times higher for bitter compounds, 2.48 times higher for amino acids, and 5.04 times higher

for glutamate salts presented alone or when mixed with the taste enhancer inosine-5′-monophosphate. Across all of these qualities, the average loss is 5.51-fold. Within each of these categories, there is considerable variability. For example, the average detection threshold for sodium carbonate is only 3.79 times higher in elderly persons than in young individuals; however, the detection thresholds for sodium succinate, sodium citrate, and sodium sulfate are 16.2, 24.5, and 28.8 times higher, respectively, in older persons. Schiffman et al (235) have found that the degree of loss is related to the molar conductivity of the anion.

Taste: Suprathreshold Losses

Suprathreshold sensitivity to taste compounds as measured by magnitude estimation and identification experiments shows a decline in elderly subjects.

MAGNITUDE ESTIMATION In magnitude estimation experiments, numbers are assigned to tastes in proportion to their perceived intensities. Applications of magnitude estimation techniques suggest that the growth in perceived intensity with increases in concentration is blunted by the aging process. Reduced suprathreshold intensities have been found for a range of common tastes including sweeteners, amino acids, and tomato juice (42, 164, 234, 240). The slopes of the lines that relate the log of the concentration (abscissa) to the perceived intensity (ordinate) for a series of sweeteners were compared for young and elderly subjects (240). The average decrement in slope with age was 48.7%; however, there was considerable variation among compounds. The greatest age-related losses in sweeteners were for thaumatin, rebaudioside, and neohesperidin dihydrochalcone, which are relatively large molecules that are capable of concerted intermolecular hydrogen bonding. There is also variability in the depression in slope for amino acids (234); the greatest depression is for glutamic and aspartic acid. This is noteworthy because alterations in glutamate binding have been found in individuals with Alzheimer's disease (93).

IDENTIFICATION TASKS Identification tasks indicate that elderly subjects are less able to identify sweet, sour, salty, and bitter compounds (29, 117) and foods that involve cooperative functioning of taste and smell (227, 228). In food tests, elderly subjects have more complaints including weakness in sensation than do young subjects (227, 228).

Taste: Causes of Perceptual Losses

The underlying physiologic changes responsible for taste decrements in the elderly are not well understood. The prevailing theory until recently was that an aged person has suffered a loss in the number of papillae and taste buds

over a lifetime. Losses in the mean number of taste buds per circumvallate papillae from adulthood to old age range from 40 to 57% (8, 185). A 20% decrease has been found in the mean number of taste buds on foliate papillae (186). The reduction in density of fungiform papillae per cm^2 on the anterior tongue of persons from 4 to 55 years of age has also been reported (190).

More recent studies contradict these earlier findings of age-related losses associated with fungiform, foliate, or circumvallate papillae. Arvidson (9) reported that there was no correlation between the number of buds per fungiform papillae and age over the life span. Studies in rhesus monkeys also show no age-related losses in buds on fungiform, foliate, or circumvallate papillae from 4 to 31 years. Further work is necessary to standardize methods of sampling, status of autopsy material, and statistical procedures before any final conclusions can be drawn. Little is known about degenerative changes in gustatory neural pathways (245).

Smell: Threshold Losses

Elderly subjects show elevated detection and recognition thresholds for olfactory and trigeminal stimulants. Threshold losses have been reported for n-butanol (149), coal gas (32, 33), coffee and citral (183), food odors (228, 242), menthol (193), pyridine and thiophene (206), 18 purified odorants (292), citralva (248), and geraniol, guaiacol, and benzaldehyde (248). The degree of loss found in elderly subjects varies widely depending on the study. However, on average, the thresholds for elderly persons in their 70s are from 2 to 10 times higher than for young persons in their 20s. Persons who are ill and are taking multiple drugs tend to have the highest thresholds.

Smell: Suprathreshold Losses

Suprathreshold losses in the sense of smell have been determined by a variety of measurement techniques including magnitude estimation, identification, and discrimination tasks. Loss in sensitivity to suprathreshold concentrations of trigeminal stimulants also occurs with age.

MAGNITUDE ESTIMATION Magnitude estimation experiments, in which numbers are assigned to odors in proportion to their perceived intensities, suggest that persons over 70 years of age perceive suprathreshold odors on average as one half as intense as persons in their 20s. Reductions in perceived intensity in older individuals have been reported for odors that range from pleasant to foul: benzaldehyde, d-limonene, pyridine, ethyl alcohol, isoamyl alcohol (280), isoamyl butyrate (279, 280, 281), menthol (193), and 8 odorants including citralva, geraniol, citronellal, 2-methoxy-3-isobutyl-pyrazine, benzaldehyde, 2-methoxypyrazine, limonene, and acetic acid (248). Losses in trigeminal sensitivity to CO_2 (281) have also been reported.

IDENTIFICATION TASKS The elderly also show a decrement in odor identification experiments. In identification tasks using 9 odors of moderate intensity (248), the scores for healthy persons over 70 years of age are from 60% to 75% of those for young subjects (248). Losses in the ability to identify coffee, peppermint, coal tar, and oil of almonds (5), a wide range of foods (194, 227), 40 common substances (226), a microencapsulated battery of 40–50 odors (57, 58), and 9 chemicals with characteristic odors (248) have been found.

DISCRIMINATION TASKS INCLUDING MULTIDIMENSIONAL SCALING TECHNIQUES Schiffman & Warwick (248) found that persons grouped by decade—10–19, 20–29, 30–39, 40–49, 50–59, 60–69, and 70–79 years—lost the ability to discriminate among 9 odors (benzaldehyde, n-butanol, caproic acid, citral, citronellal, geraniol, guaiacol, menthol, and methyl salicylate) with advancing age. The discrimination task entailed two steps, a confusability task and a similarity task. In the first (confusability) task, subjects sniffed three bottles one at a time; two of the bottles contained the same odorant. One of the six possible combinations of stimuli (AAB, ABA, ABB, BAA, BAB, and BBA) was selected randomly for each subject. In a second step, subjects considered the qualitative range for the odorants and marked the similarity of the two diferent odorants on a nine point scale from "identical" to "completely different." The confusability scores are represented as percentiles by decade in Table 5. Subjects in the seventh decade performed significantly worse than those in the younger decade groupings. It can be seen that a score of 54.2% correct would place a 75-year-old in the seventy-fifth percentile; however, the same score would relegate an 18-year-old to the first percentile. The highest score for the elderly (77.8% correct) is the average score (fiftieth percentile) for the entire group of 143 subjects.

Table 5 Percentile in which a person would be classified by decade and by subject based on percent correct score

%tile	10s	20s	30s	40s	50s	60s	70s	Composite (all decades)
99	91.7	100.0	97.2	100.0	97.2	91.7	77.8	100.0
95	91.6	99.7	96.9	99.4	96.7	91.7	77.8	94.4
90	88.9	94.4	91.7	93.9	91.1	91.7	72.8	91.7
75	85.4	91.0	88.4	87.4	88.9	83.3	54.2	86.1
50	80.6	79.2	83.3	77.8	86.1	69.4	47.2	77.8
25	75.7	72.9	66.7	63.9	68.1	66.7	38.9	61.1
10	66.9	61.8	53.1	42.2	61.6	58.3	30.3	45.5
5	64.0	61.1	50.1	29.2	58.6	50.0	23.0	39.5
1	63.9	61.1	50.0	27.8	58.3	50.0	22.2	24.7

While the confusability data suggest that persons in their 60s retain the ability to select within a triad the stimulus that differs from the other two, the similarity data indicate that these same persons have a diminished capacity to discriminate the *degree* of difference among the odorants on ratings along similarity scales. The multidimensional scaling procedure ALSCAL (individual differences option) was applied to the mean similarity matrices for each decade; these matrices were computed by averaging the ratings of each pair along the 9-point scale. Stimuli were arranged by ALSCAL so that stimuli rated similar to one another were located closer to one another than stimuli rated different from one another. Individual multidimensional spaces based on mean scores for the sixth and seventh decades indicate that subjects in the 60s and 70s have difficulty rating the degree of similarity between two different odor stimuli. However, the degree of loss in this ability is considerably greater in the 70s than in the 60s. No gender differences were found when males and females were analyzed separately.

Other multimensional scaling experiments are consistent with these findings that elderly subjects have reduced ability to discriminate suprathreshold odors. Reduced discrimination has been reported for food odors (246), common odors (278), and pyrazines (239).

Smell: Causes of Perceptual Losses

The decrements in odor perception that occur with aging can result from a variety of anatomic and physiologic losses. Structural and physiologic changes throughout the olfactory system occur in old age from the periphery (olfactory epithelium) to the olfactory bulb and to the olfactory cortex including the limbic structures. These changes include reduced protein synthesis and structural alterations in olfactory epithelium (53, 196), atrophy in olfactory bulb and nerve (25, 120, 121–124, 163, 266), presence of senile plaques and neurofibrillary tanges in hippocampus and amygdaloid complex (224, 289), hypothalamic degeneration including disruption of hypothalamic architecture paralleled by deterioration and loss of dendritic surface (165), altered calcium homeostasis in hippocampus leading to elevated intracellular calcium (155), and hippocampal pathology including increase in reactive astrocytes associated with elevated plasma adrenocorticoids (156). These structural and physiologic losses can result from normal aging, diseases, medications, and pollutants (229, 230). A theoretical model (245) based on the "across-fiber pattern" theory of Erickson (65), suggests that losses in chemosensory neurons from a variety of causes degrade the pattern of neural activity for stimuli. This degradation diminishes the ability of a person to discriminate between two stimuli.

DYSFUNCTIONS ASSOCIATED WITH ALZHEIMER'S DISEASE

Severe olfactory losses have been found in elderly persons with Alzheimer's disease (see Table 6). In 1974, Waldton (296) reported that patients with a general diagnosis of senile dementia had marked impairment of olfactory functioning and that this decrement became more severe as the disease progressed. More recent studies have found that patients with Alzheimer's disease (AD) exhibit a diminished capacity to recognize and identify supra-threshold odorants compared to that of age-matched controls. These losses in the recognition and identification of odorants are very salient in the earliest phases of the disease (153, 299). Prominent losses in the ability to remember odorants have also been reported by Moberg et al (184) in early AD. Losses in olfactory sensitivity at the threshold level tend to develop as the symptoms progress but can be present at the early stages. The degree of loss in olfactory functioning in Alzheimer's disease is greatest for olfactory memory where scores often reflect performance at the level of chance. Recognition and identification experiments indicate that persons with AD generally perform below the twenty-fifth percentile for their age group. The degree of threshold losses has not been well-established.

Decrements in olfactory perception in AD are not surprising because the morphological and neurochemical changes in this disease are especially prominent in neural pathways related to olfaction, including the olfactory epithelium (287), olfactory bulbs (202), anterior olfactory nucleus (10, 68, 141, 202), olfactory tubercle (263), amygdala (27, 119), prepiriform cortex (212), hippocampus (13, 27, 131, 141, 205), entorhinal cortex (27, 131), uncus (27), and subiculum (131). The impairment of olfactory and limbic structures of the temporal lobe produces decrements in the ability to identify, recognize, and remember odorants. Impairment closer to the periphery produces losses in the ability to detect the presence of odorants. This was clearly demonstrated by Eichenbaum et al (61) who studied the olfactory

Table 6 Deficits in Alzheimer's disease

Task	References
Recognition and identification of odors	56, 128, 148, 151–153, 204, 213, 254, 255–257, 296, 299
Odor memory	148, 184
Olfactory threshold	56, 151–153, 195, 213, 276

capacities in a patient with bilateral medial temporal lobe resection. This procedure involved bilateral removal of the amygdala, uncus, and the anterior two-thirds of the hippocampus and parahippocampal gyrus. The pyriform cortex was affected as well. This patient performed normally on a battery of tests of odor detection, intensity discrimination, and adaptation. However, the patient was unable to discriminate or identify odors in match-to-sample tasks or in same-different discriminations. Although olfactory losses do occur in other conditions that afflict the elderly, it should be emphasized here that a decrement in olfactory functioning is always associated with AD. The olfactory system may be the site of initial pathology in AD (205). Roberts (214) has suggested that the causative agent for AD may act through a nasal route. There is evidence for transneural transport in the olfactory system for such diverse materials as viruses (67, 187), dyes (133), gold (49, 133), aluminosilicates (214), and wheat-germ agglutinin-horseradish peroxidase conjugate (260). These compounds may be transported from the external environment via olfactory receptor neurons to the olfactory bulb and beyond into gustatory and other areas. This could disrupt the functioning of neurons known to be associated with AD and produce long-term changes or degeneration in these regions. The recent finding by Schiffman et al (233) that the degree of olfactory loss was related to a family history of senile dementia raises the question whether vulnerability to transneuronal transport in the olfactory system may have a genetic component.

Histopathologic changes in olfactory circuits occur in AD. However, the losses in neurotransmitters in AD may also be responsible in part for the losses in identification, recognition, and memory of odors. Neurotransmitter deficits in glutamic acid (100, 101, 173), acetylcholine (47, 132, 302), serotonin (132, 172, 304), somatostatin (215, 217), noradrenaline (16, 79, 132), and dopamine (89, 174) have been found in the brains of patients with Alzheimer's disease.

DYSFUNCTIONS ASSOCIATED WITH ENVIRONMENTAL POLLUTION

Losses in taste and smell sensations are also caused by a broad range of environmental pollutants (243). The chemical senses are especially vulnerable to environmental contaminants in water and air because taste and smell receptors are strategically situated to contact and monitor our external chemical environment. Pollutants not only produce offensive tastes and odors in and of themselves but they also damage chemosensory tissue.

Offensive Tastes and Odors Associated With Pollution

Offensive tastes and odors associated with pollution are often due to the sensory properties of the pollutants themselves rather than to pathologic changes in the chemosensory systems. For example, petroleum and petrochemical waste,

bacterial contamination of food and water, chemicals concentrated in indoor air, and industrial chemicals such as fumigants can trigger taste and smell complaints.

Sensory irritants inhaled through the nose elicit a variety of chemosensory complaints because irritants can increase permeability of blood vessels, alter secretions from mucoserous glands, alter flow patterns of nasal mucus, decrease ciliary activity on respiratory epithelial cells, and suppress breathing rate.

Persons who report hypersensitivity to airborne chemicals do not necessarily have lower taste, smell, or irritation thresholds. Rather, persons who are hypersensitive to pollutants may experience more nasal swelling and thus more irritation than normal individuals.

Pollutants That Alter the Olfactory and Taste Systems

Both acute and chronic exposure to a variety of chemical agents including industrial substances can cause losses in olfactory sensitivity. These agents include metallic compounds, nonmetallic inorganic compounds, organic compounds, dusts, and other airborne chemicals (see Table 7). Losses may occur after brief or prolonged exposure and may be either temporary or permanent. Pollutants can alter olfactory functioning in a variety of ways including modification of neurotransmitter levels and physiologic or anatomic damage to the olfactory epithelium, bulbs, or tract. Some pollutants such as methylmercury can actually accumulate in the olfactory bulbs.

Less is known about pollution-induced disturbances in taste perception. Schiffman & Nagle (243) reported that persistent metallic or bitter taste complaints occur in some individuals after exposure to insecticides. Pesticides have been shown to bind extensively to the tongue (24) and to alter taste bud morphology.

TREATMENT OR COMPENSATION FOR CHEMOSENSORY LOSSES

There are no standard treatments for chemosensory dysfunctions because little is known about the mechanisms by which they occur. While enhancement of taste or smell perception by pharmacologic means has been attempted, no studies suggest that drug treatments of any kind have broad efficacy in restoring chemosensation. Exogenous application of acetylcholine or substance P (20) apparently increases olfactory receptor cell activity, and administration of the cholinergic agonists methacholine (110) and bethanechol (11) reportedly restores taste acuity in some patients with familial dysautonomia. Dietary zinc supplementation can correct taste disorders related to zinc deficiency (169) or the zinc may combine with –SH groups in an offending molecule (e.g. captopril or D-penacillamine, see 229). However, in a controlled study, dietary supplementation with zinc sulfate was no more effective than a placebo for

Table 7 Compounds, dusts and processes associated with permanent anosmia or hyposmia in humans with chronic exposure

Compounds, dusts, and processes	References
Metallurgical compounds and processes	
Cadmium compounds including oxides	3
Chromium, including chromate salts and chromium plating	3
Lead	3
Magnet production, includes iron, aluminum, nickel, cobalt, and chromium powders	3
Mercury	3
Nickel, including nickel hydroxide, nickel plating and refining	3
Silver plating	3
Steel production	3
Zinc, including zinc chromate, zinc production	3
Dusts	
Ashes, incinerator	200
Cement	3
Chemicals	3
Coke	200
Grain	200
Hardwoods	3
Lime	3
Printing	3
Silicosis	3, 200
Nonmetallic inorganic compounds	
Ammonia	3
Carbon disulfide	3, 200
Carbon monoxide	3
Chlorine	3
Hydrazine	3
Fluorides	3
Hydrogen selenide	286
Hydrogen sulfide	1
Nitrogen dioxide (NO_2)	3
Phosphorous oxychloride	167
Sulfur dioxide	3
Organic compounds	
Acetates, butyl and ethyl	3
Acetone	3
Acetophenone	3
Acrylate and methacrylate vapors	251
Benzene	3, 200
Benzine	3
Chloromethanes (CH_3Cl, CH_2Cl_2, $CHCl_3$, CCl_4)	3
Formaldehyde	64, 88
Menthol	3, 199
Organophosphates and other insecticides	229
Pentachlorophenol	3
Petroleum	2

Table 7 (*continued*)

Compounds, dusts, and processes	References
Solvent mixtures	220, 252
Trichloroethylene	3
Manufacturing processes	
Acids (organic and inorganic)	3, 200
Asphalt (oxidized)	3
Cement works	200
Cotton, knitting factory	200
Cutting oils (machining)	3
Flour, flour mill	200
Fragrances	3
Paint	3, 252
Paper, packing factory	200
Pavinol, a synthetic leather containing dibutyl phthalate	3
Peppermint	158
Spices, including paprika	3, 200
Tobacco	3, 200
Varnishes	3
Wastewater	3

treating a wide variety of taste disorders (114). Additional research is necessary before effective pharmacologic treatments for chemosensory disorders are found.

Addition of flavors to foods for persons with hyposmia is effective in counteracting modest olfactory losses. Schiffman (228) and Schiffman & Warwick (247) reported increased preference for flavor-amplified food in the elderly. The flavors used in these experiments were mixtures of odorous molecules selected by gas chromatographic analysis of natural products. For example, mashed potatoes amplified with simulated potato flavor was preferred to unenhanced mashed potatoes. This amplification of flavor not only increased the hedonic value of foods to which it was added, but also increased intake of nutrient-dense food in sick older persons (247). It should be noted, however, that flavor amplification was not always effective. For elderly persons who are totally anosmic (such as many Alzheimer's patients), additional flavors cannot be detected.

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