26 - 35 Disorders of Smell and Taste

35 Disorders of Smell and Taste

Exaggerated gaze-evoked nystagmus can be induced by drugs (seda tives, anticonvulsants, alcohol); muscle paresis; myasthenia gravis; demyelinating disease; and cerebellopontine angle, brainstem, and cerebellar lesions. VESTIBULAR NYSTAGMUS Vestibular nystagmus results from dysfunc tion of the labyrinth (Ménière's disease, benign paroxysmal positional vertigo), vestibular nerve, or vestibular nucleus in the brainstem. Peripheral vestibular nystagmus often occurs in discrete attacks, with symptoms of nausea and vertigo. There may be associated tinnitus and hearing loss. Sudden shifts in head position may provoke or exacerbate symptoms. DOWNBEAT NYSTAGMUS Downbeat nystagmus results from lesions near the craniocervical junction (Chiari malformation, basilar invagi nation). It also has been reported in brainstem or cerebellar stroke, lith ium or anticonvulsant intoxication, alcoholism, and multiple sclerosis. Upbeat nystagmus is associated with damage to the pontine tegmentum from stroke, demyelination, or tumor. Opsoclonus This rare, dramatic disorder of eye movements con sists of bursts of consecutive saccades (saccadomania). When the saccades are confined to the horizontal plane, the term ocular flutter is preferred. It can result from viral encephalitis, trauma, or a paraneo plastic effect of neuroblastoma, breast carcinoma, and other malignan cies. It has also been reported as a benign, transient phenomenon in otherwise healthy patients. ■ ■FURTHER READING Albert DM et al: Albert and Jakobiec's Principles and Practice of Ophthalmology, 4th ed. New York, Springer Link, 2022. Apte RS: Age-related macular degeneration. N Engl J Med 385:540, 2021. Chen X et al: Shape perception via a high-channel-count neuroprosthesis in monkey visual cortex. Science 370:1191, 2020. Durand ML et al: Infectious keratitis. JAMA 326:1319, 2021. Heier JS et al: Pegcetacoplan for the treatment of geographic atrophy secondary to age-related macular degeneration (OAKS and DERBY): Two multicentre, randomised, double-masked, sham-controlled, phase 3 trials. Lancet 402:1434, 2023. Jhaveri CD: Aflibercept monotherapy or bevacizumab first for diabetic macular edema. N Engl J Med 387:692, 2022. Sahel JA: Partial recovery of visual function in a blind patient after optogenetic therapy. Nature Med 27:1223, 2021. Toth CA: Optical coherence tomography and eye care. N Engl J Med 389:1526, 2023. Yanoff M, Duker J: Ophthalmology, 6th ed. Singapore, Elsevier, 2023. Richard L. Doty, Steven M. Bromley

Disorders of Smell

and Taste All environmental chemicals necessary for life enter the body by the nose and mouth. The senses of smell (olfaction) and taste (gustation) monitor such chemicals, determine the flavor and palatability of foods and beverages, and warn of dangerous environmental conditions,

including fire, air pollution, leaking natural gas, and bacteria-laden foodstuffs. These senses contribute significantly to quality of life and, when dysfunctional, can have untoward physical and psychological consequences. A longitudinal study of 1162 nondemented elderly persons found, even after controlling for confounders, that those with the lowest baseline olfactory test scores had a 45% mortality rate over

a 4-year period, compared to an 18% mortality rate for those with the highest olfactory test scores. A basic understanding of these senses in health and disease is critical for the physician because thousands of patients present to doctors' offices each year with complaints of chemo sensory dysfunction. Among the more important recent developments in neurology is the discovery that decreased smell function is among the first signs of such neurodegenerative diseases as Parkinson's disease (PD) and Alzheimer's disease (AD), signifying their "presymptomatic" phase. ■ ■ANATOMY AND PHYSIOLOGY Disorders of Smell and Taste CHAPTER 35 Olfactory System Odorous chemicals enter the front of nose during inhalation and active sniffing, as well as the back of the nose (nasopharynx) during deglutition. After reaching the highest recesses of the nasal cavity, they dissolve in the olfactory mucus and diffuse or are actively transported by specialized proteins to receptors located on the cilia of olfactory receptor cells. The cilia, dendrites, cell bodies, and proximal axonal segments of these bipolar cells are located within a unique neuroepithelium covering the cribriform plate, the superior nasal septum, superior turbinate, and sectors of the middle turbinate (Fig. 35-1). Nearly 400 types of G-protein-coupled odor receptors (GPCRs) are expressed on the cilia of the receptor cells, with only one type of GPCR being expressed on a given cell. Other receptors, includ ing trace amine-associated receptors and members of the non-GPCR membrane-spanning 4-domain family, subfamily A (MS4A) protein family, are also present on some receptor cells. Such a plethora of recep tor cell types does not exist in any other sensory system. Importantly, when damaged, the receptor cells can be replaced by stem cells near the basement membrane, although such replacement is often incomplete. After coalescing into bundles surrounded by glia-like ensheathing cells (termed fila), the receptor cell axons pass through the cribriform plate to the olfactory bulbs, where they synapse with dendrites of other cell types within the glomeruli (Fig. 35-2). These spherical structures, which make up a distinct layer of the olfactory bulb, are a site of con vergence of information, because many more fibers enter than leave them. Receptor cells that express the same type of receptor project to the same glomeruli, effectively making each glomerulus a functional unit. The major projection neurons of the olfactory system—the mitral and tufted cells—send primary dendrites into the glomeruli, connecting not only with the incoming receptor cell axons, but with dendrites of periglomerular cells. The activity of the mitral/tufted cells is modulated by the periglomerular cells, secondary dendrites from other mitral/tufted cells, and granule cells, the most numerous cells of the bulb. The latter cells, which are largely GABAergic, receive inputs from central brain structures and modulate the output of the mitral/ tufted cells. Interestingly, like the olfactory receptor cells, some cells within the bulb undergo replacement. Thus, neuroblasts formed within the anterior subventricular zone of the brain migrate along the rostral migratory stream, ultimately becoming granule and periglomerular cells. The axons of the mitral and tufted cells synapse within secondary olfactory structures, which largely compose the primary olfactory cortex (POC) (Fig. 35-3). The POC is defined as those cortical struc tures that receive direct projections from the olfactory bulb, most nota bly the piriform and entorhinal cortices. Although olfaction is unique in that its initial afferent projections bypass the thalamus, persons with damage to the thalamus can exhibit olfactory deficits, particularly ones of odor identification. Such deficits likely reflect the involvement of thalamic connections between the

POC and the orbitofrontal cortex (OFC), where odor identification largely occurs. The close anatomic ties between the olfactory system and the amygdala, hippocampus, and hypothalamus help to explain the intimate associations between odor perception and cognitive functions such as memory, motivation, arousal, autonomic activity, digestion, and sex. Taste System Tastants are sensed by specialized receptor cells present within taste buds—small grapefruit-like segmented structures located on the lateral margins and dorsum of the tongue, roof of the mouth, pharynx, larynx, and superior esophagus (Fig. 35-4). Lin gual taste buds are embedded in well-defined protuberances, termed

PART 2 Cardinal Manifestations and Presentation of Diseases FIGURE 35-1 Anatomy of the nose, showing the distribution of olfactory receptors in the roof of the nasal cavity. (Copyright David Klemm, Faculty and Curriculum Support [FACS], Georgetown University Medical Center.) fungiform, foliate, and circumvallate papillae. After dissolving in a liquid, tastants enter the opening of the taste bud—the taste pore—and bind to receptors on microvilli, small extensions of receptor cells within each taste bud. Such binding changes the electrical potential across the taste cell, resulting in neurotransmitter release onto the first-order taste neurons. Although humans have ~7500 taste buds, not all harbor taste-sensitive cells; some contain only one class of receptor (e.g., cells responsive only to sugars), whereas others contain cells sensitive to more than one class. The number of taste receptor cells per taste bud ranges from zero to well over 100. A small family of three GPCRs, Olfactory bulb Granule cell Mitral/tufted cell Periglomerular cell Glomerulus Cribriform plate Olfactory neurons Olfactory receptor cells Supporting cell Olfactory cilia FIGURE 35-2 Schematic of the layers and wiring of the olfactory bulb. Each receptor type (red, green, blue) projects to a common glomerulus. The neural activity within each glomerulus is modulated by periglomerular cells. The activity of the primary projection cells, the mitral and tufted cells, is modulated by granule cells, periglomerular cells, and secondary dendrites from adjacent mitral and tufted cells. (Adapted from https://medicine.yale.edu/.)

namely T1R1, T1R2, and T1R3, mediate sweet and umami taste sensa tions. Bitter sensations, on the other hand, depend on T2R receptors, a family of ~30 GPCRs expressed on cells different from those that express the sweet and umami receptors. T2Rs sense a wide range of bitter substances but do not distinguish among them. Sour tastants are sensed by the PKD2L1 receptor, a member of the transient receptor potential protein (TRP) family. Perception of salty sensations, such as induced by sodium chloride, arises from the entry of Na+ ions into the cells via specialized membrane channels, such as the amiloride-sensitive Na+ channel. It is now well established that both bitter and sweet taste-related receptors are also present elsewhere in the body, most notably in the alimentary and respiratory tracts. This important discovery general izes the concept of taste-related chemoreception to areas of the body beyond the mouth and throat, with α-gustducin, the taste-specific G-protein α-subunit, expressed in so-called brush cells found specifi cally within the human trachea, lung, pancreas, and gallbladder. These brush cells are rich in nitric oxide (NO) synthase, known to defend against xenobiotic organisms, protect the mucosa from acid-induced Olfactory bulb Olfactory tract Medial olfactory stria Lateral olfactory stria Amygdala Pyriform area Entorhinal area Vagus nerve Spinal cord Cerebellar vermis Cerebellum FIGURE 35-3 Anatomy of the base of the brain showing the primary olfactory cortex.

FIGURE 35-4 Schematic of the taste bud and its opening (pore), as well as the location of buds on the three major types of papillae: fungiform (anterior), foliate (lateral), and circumvallate

(posterior). TRC, taste receptor cell. lesions, and, in the case of the gastrointestinal tract, stimulate vagal and splanchnic afferent neurons. NO further acts on nearby cells, including enteroendocrine cells, absorptive or secretory epithelial cells, mucosal blood vessels, and cells of the immune system. Members of the T2R family of bitter receptors and the sweet receptors of the T1R family have been identified within the gastrointestinal tract and in entero endocrine cell lines. In some cases, these receptors are important for metabolism, with the T1R3 receptors and gustducin playing decisive roles in the sensing and transport of dietary sugars from the intestinal lumen into absorptive enterocytes via a sodium-dependent glucose transporter and in regulation of hormone release from gut enteroendo crine cells. In other cases, these receptors may be important for airway protection, with a number of T2R bitter receptors in the motile cilia of the human airway that respond to bitter compounds by increasing their beat frequency. One specific T2R38 taste receptor is expressed in human upper respiratory epithelia and responds to acyl-monoserine lactone quorum-sensing molecules secreted by Pseudomonas aerugi nosa and other gram-negative bacteria. Differences in T2R38 function ality, as related to TAS2R38 genotype, correlate with susceptibility to upper respiratory infections in humans. Taste information is sent to the brain via three cranial nerves (CNs): CN VII (the facial nerve, which involves the intermediate nerve with its branches, the greater petrosal and chorda tympani nerves), CN IX (the glossopharyngeal nerve), and CN X (the vagus nerve) (Fig. 35-5). CN VII innervates the anterior tongue and all of the soft palate, CN IX innervates the posterior tongue, and CN X innervates the laryngeal surface of the epiglottis, larynx, and proxi mal portion of the esophagus. The mandibular branch of CN V (V3) conveys somatosensory information (e.g., touch, burning, cooling, irritation) to the brain. Although not technically a gustatory nerve, CN V shares primary nerve routes with many of the gustatory nerve fibers and adds temperature, texture, pungency, and spiciness to the taste experience. The chorda tympani nerve is famous for taking a recurrent course through the facial canal in the petrosal portion of the temporal bone, passing through the middle ear, and then exit ing the skull via the petrotympanic fissure, where it joins the lingual nerve (a division of CN V) near the tongue. This nerve also carries parasympathetic fibers to the submandibular and sublingual glands, whereas the greater petrosal nerve supplies the palatine glands, thereby influencing saliva production.

Taste pore Taste bud Circumvallate Disorders of Smell and Taste CHAPTER 35 Taste bud TRC Foliate Taste bud Fungiform The axons of the projection cells, which synapse with taste buds, enter the rostral portion of the nucleus of the solitary tract (NTS) within the medulla of the brainstem (Fig. 35-5). From the NTS, neu rons then project to a division of the ventroposteromedial thalamic nucleus (VPM) via the medial lemniscus. From here, projections are made to the rostral part of the frontal operculum and adjoining insula, a brain region considered the primary taste cortex (PTC). Pro jections from the PTC then go to the secondary taste cortex, namely the caudolateral OFC. This brain region is involved in the conscious recognition of taste qualities. Moreover, because it contains cells that are activated by several sensory modalities, it is likely a center for establishing “flavor.” FIGURE 35-5 Schematic of the cranial nerves (CNs) that mediate taste function, including the chorda tympani nerve (CN VII), the glossopharyngeal nerve (CN IX), and the vagus nerve (CN X). (Copyright David Klemm, Faculty and Curriculum Support [FACS], Georgetown University Medical Center.)

■ ■DISORDERS OF OLFACTION The ability to smell is influenced, in everyday life, by such factors as age, gender, general health, nutrition, smoking, and reproductive state. Women typically

outperform men on tests of olfactory function and retain normal smell function to a later age than do men.

Estimates of the prevalence of olfactory dysfunction in the general population vary; a cross-sectional analysis from the National Health and Nutrition Examination Survey (NHANES 2013–2014) found an overall prevalence of 13.5%. However, it is apparent that significant decrements in the ability to smell are present in >50% of the popula tion between 65 and 80 years of age and in 75% of those aged ≥80 years (Fig. 35-6). Such presbyosmia helps to explain why many elderly patients report that food has little flavor, a problem that can result in nutritional disturbances. This also helps to explain why a dispropor tionate number of elderly people die in accidental gas poisonings. A relatively complete listing of conditions and disorders that have been associated with olfactory dysfunction is presented in Table 35-1. PART 2 Cardinal Manifestations and Presentation of Diseases Aside from aging, the three most common identifiable causes of long-lasting or permanent smell loss seen in the clinic are, in order of frequency, severe upper respiratory infections, head trauma, and chronic rhinosinusitis. The physiologic basis for most head MALE NORMS: PERCENTILE VALUES Age of Examinee 5–9 10–14 15–19 20–24 25–29 30–34 35–39 40–44 45–49 50–54 55–59 60–64 65–69 70–74 75–79 80–84 ≥85

NORMOSMIA NORMOSMIA MILD MICROSMIA MILD MICROSMIA MODERATE MICROSMIA MODERATE MICROSMIA SEVERE MICROSMIA SEVERE MICROSMIA Test Score PROBABLE MALINGERING PROBABLE MALINGERING

N = FIGURE 35-6 Scores on the University of Pennsylvania Smell Identification Test (UPSIT) as a function of subject age and sex. Numbers by each data point indicate sample sizes. Women identify odorants better than men at all ages. (Reproduced with permission from RL Doty. Measurement of chemosensory function. WJOHNS 4:11-28, 2018.)

trauma–related losses is the shearing and subsequent scarring of the olfactory fila as they pass from the nasal cavity into the brain cavity. The cribriform plate does not have to be fractured or show pathology for smell loss to be present. Severity of trauma, as indexed by a poor Glasgow Coma Scale score on presentation and the length of posttrau matic amnesia, is associated with higher risk of olfactory impairment. Less than 10% of posttraumatic anosmic patients will recover age-related normal function over time. This increases to nearly 25% of those with less-than-total loss. Respiratory infections, such as those associated with the common cold, influenza, pneumonia, HIV, and COVID-19, can directly and permanently damage the olfactory epithelium, decreas ing receptor cell number, damaging cilia on remaining receptor cells, and inducing the replacement of sensory epithelium with respiratory epithelium. The smell loss associated with chronic rhinosinusitis is related to disease severity, with most loss occurring in cases where rhinosinusitis and polyposis are both present. Smell loss is among the first signs of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which is responsible for COVID-19. In most cases, this loss is independent of nasal inflammation. Many of those afflicted are unaware of their deficit until objectively tested. Failure to regain normal olfactory function occurs in up to 30% even a year after ANOSMIA ANOSMIA

TABLE 35-1 Disorders and Conditions Associated with Compromised Olfactory Function, as Measured by Olfactory Testing Endocrine and Metabolic Conditions Adrenal cortical insufficiency

(Addison’s disease) Chromatin-negative gonadal dysgenesis (Turner’s syndrome) Cushing’s syndrome Diabetes Hypertension Hypothyroidism Idiopathic hypogonadotropic hypogonadism Kallmann’s syndrome Liver disease Renal disease/kidney failure Pregnancy Pseudohypoparathyroidism Wilson’s disease Nasosinus Disorders Adenoid hypertrophy Bacterial and viral upper respiratory infections Laryngopharyngeal reflux disease Rhinosinusitis/polyposis Neurologic Diseases/Disorders Alzheimer’s disease Amyotrophic lateral sclerosis (ALS) Bell’s palsy Degenerative ataxias Down’s syndrome Epilepsy Facial paralysis Fibromyalgia Frontotemporal lobe degeneration Guamanian ALS/Parkinson’s disease/dementia syndrome Head trauma Huntington’s disease Idiopathic inflammatory myopathies Korsakoff psychosis Lubag disease Migraine Multi-infarct dementia Narcolepsy with cataplexy Neoplasms, cranial/nasal Orthostatic tremor Parkinson’s disease Pick’s disease Rapid eye movement behavioral sleep disorder Stroke Immune-Related Diseases Acute disseminated encephalomyelitis Allergic rhinitis Asthma Autoimmune pancreatitis Behçet’s disease Churg-Strauss syndrome Cystic fibrosis Fibromyalgia Giant cell arteritis Hereditary angioedema Idiopathic inflammatory myopathies Inflammatory bowel diseases Lupus Mikulicz’s disease Multiple sclerosis Myasthenia gravis Neuromyelitis optica Pemphigus vulgaris Psoriasis vulgaris Rheumatoid arthritis Sjögren’s syndrome Systemic sclerosis (scleroderma) Wegener’s granulomatosis Psychiatric-Related Diseases/Disorders Anorexia nervosa Asperger’s syndrome Attention deficit/hyperactivity disorder Depression Obsessive compulsive disorder Panic disorder Posttraumatic stress disorder Psychopathy Schizophrenia Seasonal affective disorder 22q11 deletion syndrome Note: These disease/disorder classifications are not necessarily mutually exclusive. diagnosis, with 5–10% experiencing total loss. Although in rhinosi nusitis cases systemic glucocorticoid therapy can usually induce shortterm functional improvement, it does not, on average, return smell test scores to normal, implying that chronic permanent neural loss is present and/or that short-term administration of systemic glucocorticoids does not completely mitigate the inflammation. It is well established that microinflammation in an otherwise seemingly normal epithelium can influence smell function. A number of neurodegenerative diseases are accompanied by olfactory impairment, including PD, AD, Huntington’s disease, parkinsonism-

dementia complex of Guam, dementia with Lewy bodies (DLB), multiple system atrophy, corticobasal degeneration, frontotemporal dementia, and Down’s syndrome; smell loss can also occur in idio pathic rapid eye movement (REM) behavioral sleep disorder (iRBD), as well as in multiple sclerosis (MS) related to lesions within olfaction-related structures. Olfactory impairment in PD often predates the clinical diagnosis by a number of years. In staged cases, studies of the sequence of formation of abnormal α-synuclein aggregates and Lewy bodies

Viral, Bacterial, and Fungal Infections Candidiasis COVID-19 Hepatitis C Herpetic meningoencephalitis Human immunodeficiency virus Legionnaires’ disease Leprosy (Hansen’s disease) Lyme disease Poliomyelitis Rhinosinusitis Upper respiratory infections Disorders of Smell and Taste CHAPTER 35 Other Disorders or Factors Alcoholism Bardet-Biedl syndrome Chemical exposure Congenital Iatrogenesis, including chemotherapy and radiation Nutritional deficiencies Obesity Tobacco smoking Toxic chemical exposures Vitamin B12 deficiency suggest that the olfactory bulbs may be, along with the dorsomotor nucleus of the vagus, the first site of neural damage in PD. In postmor tem studies of patients with very mild “presymptomatic” signs of AD, poorer smell function has been associated with higher levels of AD-related pathology. Smell loss is more marked in patients with early clinical manifestations of DLB than in those with mild AD. Interestingly, smell loss is minimal or nonexistent in progressive supranuclear palsy and 1-methyl-

4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism. The relative contributions of disease-specific pathology or differential damage to forebrain neuromodulator/neurotransmitter systems in explaining different degrees of olfactory dysfunction among the various neurodegenerative diseases are presently unknown. The smell loss seen in iRBD is of the same magnitude as that found in PD. This is of particular interest because patients with iRBD fre quently develop PD and hyposmia. REM behavior disorder is not only seen in its idiopathic form but can also be associated with narcolepsy (Chap. 33). A study of narcoleptic patients with and without REM behavior disorder demonstrated that narcolepsy, independent of REM

behavior disorder, was associated with impairments in olfactory func tion. Loss of hypothalamic neurons expressing orexin (also known as hypocretin) neuropeptides is believed to be responsible for narcolepsy and cataplexy. Orexin-containing neurons project throughout the entire olfactory system (from the olfactory epithelium to the olfac tory cortex), and damage to these projections may be one underlying mechanism for impaired olfactory performance in narcoleptic patients. Administration of intranasal orexin A (hypocretin-1) improved olfac tory function, supporting the notion that mild olfactory impairment is not only a primary feature of narcolepsy with cataplexy, but that orexin deficiency may be directly responsible for the loss of smell in this condition.

PART 2 Cardinal Manifestations and Presentation of Diseases ■ ■DISORDERS OF TASTE The majority of patients who present with taste dysfunction exhibit olfactory, not taste, loss. This is because most flavors attributed to taste actually depend on retronasal stimulation of the olfactory receptors during deglutition. As noted earlier, taste buds only mediate basic tastes such as sweet, sour, bitter, salty, and umami. Significant impair ment of whole-mouth gustatory function is rare outside of generalized metabolic disturbances or systemic use of some medications, because taste bud regeneration occurs and peripheral damage alone would require the involvement of multiple CN pathways. Taste function can be influenced by age, diet, smoking behavior, use of medications, and other subject-related factors including (1) the release of foul-tasting materials from the oral cavity from oral medical conditions (e.g., gingivitis, purulent sialadenitis) or appliances; (2) transport problems of tastants to the taste buds (e.g., drying, infections, or inflammatory conditions of the orolingual mucosa), (3) damage to the taste buds themselves (e.g., local trauma, invasive carcinomas), (4) damage to the neural pathways innervating the taste buds (e.g., middle ear infec tions), (5) damage to central structures (e.g., multiple sclerosis, tumor, epilepsy, stroke), and (6) systemic disturbances of metabolism (e.g., diabetes, thyroid disease, medications). Unlike CN VII, CN IX is relatively protected along its path, although iatrogenic interventions such as tonsillectomy, bronchoscopy, laryn goscopy, endotracheal intubation, and radiation therapy can result in selective injury. CN VII damage commonly results from mastoidec tomy, tympanoplasty, and stapedectomy, in some cases inducing per sistent metallic sensations. Bell’s palsy (Chap. 452) is one of the most common causes of CN VII injury that results in taste disturbance. On rare occasions, migraine (Chap. 441) is associated with a gustatory prodrome or aura, and in some cases, tastants can trigger a migraine attack. Interestingly, dysgeusia occurs in some cases of burning mouth syndrome (also termed glossodynia or glossalgia), as does dry mouth and thirst. Burning mouth syndrome is likely associated with dysfunc tion of the trigeminal nerve (CN V). Some of the etiologies suggested for this poorly understood syndrome are amenable to treatment, including (1) nutritional deficiencies (e.g., iron, folic acid, B vitamins, zinc), (2) diabetes mellitus (possibly predisposing to oral candidiasis), (3) denture allergy, (4) mechanical irritation from dentures or oral devices, (5) repetitive movements of the mouth (e.g., tongue thrust ing, teeth

grinding, jaw clenching), (6) tongue ischemia as a result of temporal arteritis, (7) periodontal disease, (8) reflux esophagitis, and (9) geographic tongue. Although both taste and smell can be adversely influenced by drugs, taste alterations are more common. Indeed, >250 medications have been reported to alter the ability to taste. Major offenders include antineoplastic agents, antirheumatic drugs, antibiotics, and blood pres sure medications. Terbinafine, a commonly used antifungal, has been linked to taste disturbance lasting up to 3 years. In a recent controlled trial, nearly two-thirds of individuals taking eszopiclone (Lunesta) for insomnia experienced a bitter dysgeusia that was stronger in women, systematically related to the time since drug administration, and posi tively correlated with both blood and saliva levels of the drug. Intra nasal use of nasal gels and sprays containing zinc, which are common over-the-counter prophylactics for upper respiratory viral infections, has been implicated in loss of smell function. Whether their efficacy in preventing such infections, which are the most common cause of

anosmia and hyposmia, outweighs their potential detriment to smell function requires study. Dysgeusia occurs commonly in the context of drugs used to treat or minimize symptoms of cancer, with a weighted prevalence from 56 to 76% depending on the type of cancer treatment. Attempts to prevent taste problems from such drugs using prophylac tic zinc sulfate or amifostine have proven to be minimally beneficial. Although antiepileptic medications are occasionally used to treat smell or taste disturbances, the use of topiramate has been reported to result in a reversible loss of an ability to detect and recognize tastes and odors during treatment. As with olfaction, a number of systemic disorders can affect taste. These include, but are not limited to, chronic renal failure, end-stage liver disease, vitamin and mineral deficiencies, diabetes mellitus, and hypothyroidism. In diabetes, there appears to be a progressive loss of taste beginning with glucose and then extending to other sweeteners, salty stimuli, and then all stimuli. Psychiatric conditions can be associ ated with chemosensory alterations (e.g., depression, schizophrenia, bulimia). A recent review of tactile, gustatory, and olfactory hallucina tions demonstrated that no one type of hallucinatory experience is pathognomonic to any given diagnosis. Pregnancy is a unique condition with regard to taste function. There appears to be an increase in dislike and intensity of bitter tastes during the first trimester that may help to ensure that pregnant women avoid poisons during a critical phase of fetal development. Similarly, a rela tive increase in the preference for salt and bitter in the second and third trimesters may support the ingestion of much-needed electrolytes to expand fluid volume and support a varied diet. ■ ■CLINICAL EVALUATION In most cases, a careful clinical history will establish the probable etiol ogy of a chemosensory problem, including questions about its nature, onset, duration, and pattern of fluctuations. Sudden loss suggests the possibility of head trauma, ischemia, infection, or a psychiatric condition. Gradual loss can reflect the development of a progressive obstructive lesion, although gradual loss can also follow head trauma. Intermittent loss suggests the likelihood of an inflammatory process. The patient should be asked about potential precipitating events, such as cold or flu infections, prior to symptom onset, because these often go underappreciated. Information regarding head trauma, smoking habits, drug and alcohol abuse (e.g., intranasal cocaine, chronic alco holism), exposures to pesticides and other toxic agents, and medical interventions is also informative. A determination of all the medica tions that the patient was taking before and at the time of symptom onset is important because many can cause chemosensory distur bances. Comorbid medical conditions associated with smell impair ment, such as renal failure, liver disease, hypothyroidism, diabetes, or dementia, should be assessed. Delayed puberty in association with anosmia (with or without midline craniofacial abnormalities, deafness, and renal anomalies) suggests the possibility of Kallmann’s syndrome.

Recollection of epistaxis, discharge (clear, purulent, or bloody), nasal obstruction, allergies, and somatic symptoms, including headache or irritation, may have localizing value. Questions related to memory, par kinsonian symptoms, and seizure activity (e.g., automatisms, blackouts, auras, déjà vu) should be posed. Pending litigation and the possibility of malingering should be considered. Modern forced-choice olfactory tests can detect malingering from improbable responses. Neurologic and otorhinolaryngologic (ORL) examinations, along with appropriate brain and nasosinus imaging, aid in the evaluation of patients with olfactory or gustatory complaints. The neural evaluation should focus on CN function, with particular attention to possible skull base and intracranial lesions. Visual acuity, field, and optic disc exami nations aid in detection of intracranial mass lesions that produce raised intracranial pressure (papilledema) and optic atrophy. Foster Kennedy syndrome refers to raised intracranial pressure plus a compressive optic neuropathy; typical causes are olfactory groove meningiomas or other frontal lobe tumors. The ORL examination should thoroughly assess the intranasal architecture and mucosal surfaces. Polyps, masses, and adhesions of the turbinates to the septum may compromise the flow of air to the olfactory receptors, because less than a fifth of the inspired

air traverses the olfactory cleft in the unobstructed state. Blood tests may be helpful to identify such conditions as diabetes, infection, heavy metal exposure, nutritional deficiency (e.g., vitamin B6 or B12), allergy, and thyroid, liver, and kidney disease. As with other sensory disorders, quantitative sensory testing is advised. Self-reports of patients can be misleading, and some patients who complain of chemosensory dysfunction have normal function for their age and gender. Quantitative smell and taste testing provides objective information for worker’s compensation and other legal claims, as well as a way to accurately assess the effects of treatment interven tions. A number of standardized olfactory and taste tests are com mercially available. The most widely used olfactory test, the 40-item University of Pennsylvania Smell Identification Test (UPSIT), uses norms based on over 10,000 normal subjects. A determination is made of both absolute dysfunction (i.e., mild loss, moderate loss, severe loss, total loss, probable malingering) and relative dysfunction (percentile rank for age and gender). Although electrophysiologic testing is avail able at some smell and taste centers (e.g., odor event-related potentials), they require complex stimulus presentation and recording equipment and rarely provide additional diagnostic information. With the excep tion of electrogustometers, commercially available taste tests have only recently become available. Most use filter paper strips or similar materi als impregnated with tastants, so no stimulus preparation is required. ■ ■TREATMENT AND MANAGEMENT Given the various mechanisms by which olfactory and gustatory distur bance can occur, management of patients tends to be condition-specific. For example, patients with hypothyroidism, diabetes, or infections often benefit from specific treatments to correct the underlying disease process that is adversely influencing chemoreception. For most patients who present primarily with obstructive/transport loss affecting the nasal and paranasal regions (e.g., allergic rhinitis, polyposis, intranasal neoplasms, nasal deviations), medical and/or surgical intervention is often beneficial. Antifungal and antibiotic treatments may reverse taste problems secondary to candidiasis or other oral infections. Chlorhexi dine mouthwash mitigates some salty or bitter dysgeusias, conceivably as a result of its strong positive charge. Excessive dryness of the oral mucosa is a problem with many medications and conditions, and arti ficial saliva (e.g., Xerolube) or oral pilocarpine treatments may prove beneficial. Other methods to improve salivary flow include the use of mints, lozenges, or sugarless gum. Flavor enhancers may make food more palatable (e.g., monosodium glutamate), but caution is advised to avoid overusing ingredients containing

sodium or sugar, particularly in circumstances when a patient also has underlying hypertension or diabetes. Medications that induce distortions of taste can often be dis continued and replaced with other types of medications or modes of therapy. As mentioned earlier, pharmacologic agents result in taste dis turbances much more frequently than smell disturbances. It is impor tant to note, however, that many drug-related effects are long lasting and not reversed by short-term drug discontinuance. A study of endoscopic sinus surgery in patients with chronic rhi nosinusitis and hyposmia revealed that patients with severe olfactory dysfunction prior to the surgery had a more dramatic and sustained improvement over time compared to patients with more mild olfactory dysfunction prior to intervention. In the case of intranasal and sinus-

related inflammatory conditions, such as seen with allergy, viruses, and traumas, the use of intranasal or systemic glucocorticoids may also be helpful. One common approach is to use a tapering course of oral pred nisone. Topical intranasal administration of glucocorticoids was found to be less effective in general than systemic administration; however, the effects of different nasal administration techniques were not analyzed. For example, intranasal glucocorticoids are more effective if adminis tered in the Moffett's position (head in the inverted position such as over the edge of the bed with the bridge of the nose perpendicular to the floor). After head trauma, an initial trial of glucocorticoids may help to reduce local edema and the potential deleterious deposition of scar tissue around olfactory fila at the level of the cribriform plate. Treatments are limited for patients with chemosensory loss or pri mary injury to neural pathways. Nonetheless, spontaneous recovery

can occur. In a follow-up study of 542 patients presenting to our center with smell loss from a variety of causes, modest improvement occurred over an average time period of 4 years in about half of the participants. However, only 11% of the anosmic and 23% of the hyposmic patients regained normal age-related function. Interestingly, the amount of dys function at the time of presentation, not etiology, was the best predictor of prognosis. Other predictors were age and the duration of dysfunc tion prior to initial testing.

Several studies have reported that patients with hyposmia may benefit from repeated smelling of odors over the course of weeks or months, although it remains to be determined how much improve ment, if any, occurs over that known to occur spontaneously. The usual paradigm is to smell odors such as eucalyptol, citronella, eugenol, and phenyl ethyl alcohol before going to bed and immediately upon awak ening each day. The rationale for such an approach comes from animal studies demonstrating that prolonged exposure to odorants can induce increased neural activity within the olfactory bulb. There is also limited evidence that α-lipoic acid (400 mg/d), an essential cofactor for many enzyme complexes with possible antioxidant effects, may be beneficial in mitigating smell loss following viral infection of the upper respira tory tract. However, double-blind studies are needed to confirm this observation. α-Lipoic acid has also been suggested to be useful in some cases of hypogeusia and burning mouth syndrome. Disorders of Smell and Taste CHAPTER 35 The use of zinc and vitamin A in treating olfactory disturbances is controversial, and there does not appear to be much benefit beyond replenishing established deficiencies. However, zinc has been shown to improve taste function secondary to hepatic deficiencies, and retinoids (bioactive vitamin A derivatives) are known to play an essential role in the survival of olfactory neurons. One protocol in which zinc was infused with chemotherapy treatments suggested a possible protective effect against developing taste impairment. Diseases of the alimentary tract

can not only influence chemoreceptive function but also occa sionally influence vitamin B12 absorption. This can result in a relative deficiency of vitamin B12, theoretically contributing to olfactory nerve disturbance. Vitamin B2 (riboflavin) and magnesium supplements are reported in the alternative literature to aid in the management of migraine that, in turn, may be associated with smell dysfunction. Because vitamin D deficiency is a cofactor of chemotherapy-induced mucocutaneous toxicity and dysgeusia, adding vitamin D3, 1000–2000 units per day, may benefit some patients with smell and taste complaints during or following chemotherapy. A number of medications have reportedly been used with success in ameliorating olfactory symptoms, although strong scientific evidence for efficacy is generally lacking. A report that theophylline improved smell function was uncontrolled and failed to account for the fact that some meaningful improvement occurs without treatment; indeed, the per centage of responders was about the same (~50%) as that noted by others to show spontaneous improvement over a similar time period. Anti epileptics and some antidepressants (e.g., amitriptyline) have been used to treat dysosmias and smell distortions, particularly following head trauma. Ironically, amitriptyline is also frequently on the list of medica tions that can ultimately distort smell and taste function, possibly from its anticholinergic effects. One study suggested that the centrally acting acetylcholinesterase inhibitor donepezil in AD resulted in improve ments on smell identification measures that correlated with overall clinician-based impressions of change in dementia severity scores. Alternative therapies, such as acupuncture, meditation, cognitive-

behavioral therapy, and yoga, can help patients manage uncomfortable experiences associated with chemosensory disturbance and oral pain syndromes and to cope with the psychosocial stressors surrounding the impairment. Additionally, modification of diet and eating habits is also important. By accentuating the other sensory experiences of a meal, such as food texture, aroma, temperature, and color, one can optimize the overall eating experience for a patient. In some cases, a flavor enhancer like monosodium glutamate (MSG) can be added to foods to increase palatability and encourage intake. Proper oral and nasal hygiene and routine dental care are extremely important ways for patients to protect themselves from disorders of the mouth and nose that can ultimately result in chemosensory

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