in PD. In postmortem 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. In MS, the olfactory disturbance varies as a function of the plaque activity within the frontal and temporal lobes.

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 frequently develop PD and hyposmia. There is some evidence that iRBD may actually represent an early associated condition of PD. REM behavior disorder is not only seen in its idiopathic form, but can also be associated with narcolepsy. This led to a recent study of narcoleptic patients with and without REM behavior disorder, which demonstrated that narcolepsy, independent of REM behavior disorder, was associated with impairments in olfactory function. Orexin A, also known as hypocretin-1, is dramatically diminished or undetectable in the cerebrospinal fluid of patients with narcolepsy and cataplexy **(Chap. 38)**. The orexin-containing neurons in the hypothalamus project throughout the entire olfactory system (from the olfactory epithelium to the olfactory cortex), and damage to these orexin-containing projections may be one underlying mechanism for impaired olfactory performance in narcoleptic patients. The administration of intranasal orexin A (hypocretin-1) appears to result in improved olfactory function, supporting the notion that mild olfactory impairment is not only a primary feature of narcolepsy with cataplexy, but that central nervous system orexin deficiency may be a fundamental part of the mechanism for this loss.

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 impairment 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 cranial nerve pathways. Nonetheless, taste can be influenced by (1) the release of foul-tasting materials from the oral cavity from oral medical conditions or appliances (e.g., gingivitis, purulent sialadenitis), (2) transport problems of tastants to the taste buds (e.g., drying of the orolingual mucosa, infections, inflammatory conditions), (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 infections), (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, laryngoscopy, endotracheal intubation, and radiation therapy can result in selective injury. CN VII damage commonly results from mastoidectomy, tympanoplasty, and stapedectomy, in some cases inducing persistent metallic sensations. Bell's palsy **(Chap. 455)** is one of the most common causes of CN VII injury that results in taste disturbance. On rare occasions, migraines **(Chap. 447)** are 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 (BMS; also termed *glossodynia* or *glossalgia*), as do dry mouth and thirst. BMS is likely associated with dysfunction 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 thrusting, 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 pharmacologic agents, drug-related taste alterations are more common. Indeed, over 250 medications have been reported to alter the ability to taste. Major offenders include antineoplastic agents, antirheumatic drugs, antibiotics, and blood pressure 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) experienced a bitter dysgeusia that was stronger in women, systematically related to the time since drug administration, and positively correlated with both blood and saliva levels of the drug. Intranasal 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 56–76% depending on the type of cancer treatment. Attempts to prevent taste problems from such drugs using prophylactic 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 chronic renal failure, end-stage liver disease, vitamin and mineral deficiencies, diabetes mellitus, and hypothyroidism (to name a few). 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 associated with chemosensory alterations (e.g., depression, schizophrenia, bulimia). A recent review of tactile, gustatory, and olfactory hallucinations demonstrated that no one type of hallucinatory experience is pathognomonic to any given diagnosis.

Pregnancy proves to be 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 relative 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 etiology 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. *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 alcoholism in the context of Wernicke's and Korsakoff's syndromes), exposures to pesticides and other toxic agents, and medical interventions is also informative. A determination of all the medications that the patient was taking before and at the time of symptom onset is important, because many can cause chemosensory disturbances. Comorbid medical conditions associated with smell impairment, 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, parkinsonian signs, and seizure activity (e.g., automatisms, blackouts,