Handbook of Olfaction and Gustation

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Evaluation of Olfactory Deficits by Structural Medical Imaging

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I. INTRODUCTION

Olfactory dysfunction can generally be classified into (1) conductive disorders caused by interference with the access of odorants to the olfactory receptors, (2) peripheral sensorineural disorders resulting from injury to the olfactory receptors (within the olfactory mucosa), and (3) central neural disorders of the olfactory bulb or tract or related parts of the central nervous system such as the prefrontal lobe, septal nuclei, amygdala, and temporal lobe. For medical imaging and the anatomical approach, we categorize olfactory dysfunction into two major groups: peripheral causes—sinonasal tract disorders—and central causes— intracranial disorders. It is important to relate olfactory deficits to the appropriate anatomical and pathological changes. Unfortunately, clinical olfactory testing, whether psychophysical or electrophysiological, is rarely capable of localizing the source (aside from determining whether it is on the right or left) or identifying the specific cause of decreased smell function.

Modern medical imaging techniques offer a valuable means for assessing the basis of some disorders of olfaction. Although revolutionary changes in medical imaging techniques have occurred in the last few decades, only a few articles have dealt with imaging studies related to chemosensory disorders (Doty et al., 1999; Goodspeed et al., 1987; Kimmelman, 1991; Klingmuller et al., 1987; Li et al., 1994; Schellinger et al., 1983; Yousem et al., 1996, 1997, 1998, 1999). In this chapter we comprehensively review the pertinent medical literature on this general topic and detail our own experience.

II. IMAGING MODALITIES AND TECHNIQUES

Major advances in pinpointing the anatomical and pathological changes of many disorders of the sinonasal cavity and brain have become possible as a result of the development and refinement of imaging techniques (Carter and Runge, 1988; Healy, 1992; Jagust and Eberling, 1991; Jolles et al., 1989; Reiman and Mintun, 1990; Shapiro and Som, 1989; Vogl, 1990; Yousem et al. 1996a, 1997b, 1998). Even though the imaging evaluation is not the diagnostic equivalent to histological study, anatomical imaging, such as high-resolution computed tomography (CT) and magnetic resonance imaging (MRI), can not only map regional lesions, but may also suggest a differential diagnosis (Carter and Runge, 1988; Shapiro and Son, 1989; Som and Shapiro, 1988). On the other hand, functional imaging (PET, SPECT, fMRI), which is reviewed in Chapter 12, affords one the potential to explore regional pathophysiological changes in the living brain (Healy, 1992; Jagust and Eberling, 1991; Jolles et al., 1989; Reiman and Mintun, 1990; Yousem et al., 1997b, 1999b, c). The relevant imaging modalities which may be helpful in the evaluation of common causes of olfactory deficits are reviewed in this section.

A. Plain Radiographs

Plain film radiography, i.e., the "sinus series," including the Caldwell view, the Waters view, the lateral view, and the base view, has long been a standard method of diagnosing nasal and paranasal sinus inflammatory disease. Problems of overlap and nonspecific findings are impossible to avoid with plain films, and thus the study has been largely replaced by CT. The most important deficit of the plain film is its inability to provide the road map of the ostiomeatal complex, which may guide endoscopic surgical intervention (Zinreich et al., 1987). Plain radiographs and conventional plain film tomography have virtually no role in the imaging evaluation of olfactory dysfunction.

B. Computed Tomography

CT is well suited to the investigation of the sinonasal cavities. Because CT scanning is as sensitive to soft tissue disease as to bony changes, each scan can be photographed at an appropriate window width and level to optimally see insidious soft tissue differences in attenuation and fine bony detail. To study soft tissue, the window widths range from 150 to 400 Hounsfield units. Conversely, the bony detail is best observed at wide window settings—from 2000 to 4000 Hounsfield units. The basic CT scanning protocol should include all of the nasal cavity, paranasal sinuses, hard plate, anterior skull base, orbits, and nasopharynx. The brain should be included if central causes of olfactory dysfunction are suspected. The scans are commonly performed in both the axial and coronal planes for optimal assessment of the complex paranasal anatomy, but coronal scans are the most valuable for the anterior naso-ethmoid (ostiomeatal) region. Alternatively, thin sections in one plane with multiplanar reconstructions may be adequate. For practical purposes, slice thicknesses of 3–5 mm are often employed. For the evaluation of the ostiomeatal complex (the maxillary sinus ostium, infundibulum, uncinate process, and middle meatus), 3-mm-thick coronal sections are fairly standard unless three-dimensional (3D) reconstructions are requested. The quality of the 3D images is improved by utilizing 1-mm-thick sectioning, which is rapidly performed with the new spiral scanners (minutes) and multidetector scanners (seconds). Intravenous contrast enhancement is usually reserved for the identification of vascular lesions, tumors, meningeal or parameningeal processes, and abscess cavities (Carter and Runge, 1988). Intrathecal contrast may be employed when cerebrospinal fluid leaks accompany the olfactory deficits. High-resolution CT is the most useful and cost-effective screening tool for the evaluation of sinonasal tract inflammatory disorders.

C. Magnetic Resonance Imaging

MRI's multiplanar capability is especially advantageous in the evaluation of sinonasal tract neoplasms and brain disorders. MRI, however, is less sensitive for the detection of bony cortical abnormalities and landmarks. Soft tissue discrimination, on the other hand, is more clearly illustrated by MRI than by CT. Most soft tissue disease processes can be accurately localized with a minor degree of tissue differentiation, i.e., infection vs. tumor vs. hemorrhage. The anatomical discrimination of the brain is much better using MRI than CT. One can use thin sections, large matrices, and smaller fields of view to improve resolution, yet maintain, high contrast to noise using T_1-weighted scans (T_1W) or fast spin echo T_2-weighted (T_2W) images. T_2-weighted scans can better delineate the contrast between normal and inflammatory or neoplastic tissue (Shapiro and Som, 1989). New phase sensitive inversion recovery pulse sequences or standard spoiled gradient echo sequences can highlight the gray-white matter differentiation and allow better assessment of the hippocampus, parahippocampus, gyrus rectus, and entorhinal cortex regions. Segmentation of images to separate cortical volume from whole brain volume is customary for volumetric studies nowadays.

For the evaluation of skull base invasion by sinonasal tumors, MRI is superior to CT (Paling et al., 1987). Gadolinium enhanced scans are particularly useful at the skull base to detect dural or leptomeningeal involvement. Gadolinium-DTPA, a paramagnetic contrast agent, has been widely utilized for distinguishing solidly enhancing tumor from rim-enhancing inflammatory processes (Brasch, 1992; Vogl et al., 1990).

With regard to the olfactory system, CT and MRI play complementary roles in evaluating sinonasal tract neoplasms (Shapiro and Som, 1989; Som et al., 1990). However, MRI is the study of choice to directly visualize the olfactory bulbs, olfactory tracts, and intracranial causes of olfactory dysfunction (Klingmuller et al., 1987; Suzuki et al., 1989; Yousem et al., 1993, 1998, 1999a).

D. Nuclear Medicine

In general, conventional radionuclide imaging plays no significant role in the diagnostic work-up of patients with suspected sinonasal tract disease (peripheral causes of olfactory deficits), except in the case of cerebrospinal fluid (CSF) leaks. Functional imaging studies, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT), are valuable in detecting alterations of regional brain function and biochemistry in vivo (Alavi & Hirsch, 1991; Fowler et al., 1988; Jagust and Eberling, 1991; Jolles et al., 1989; Reman and Mintun,

1990). Recent studies have suggested that functional imaging is more sensitive than anatomical imaging in detecting abnormalities of the brain related to disorders such as Alzheimer's disease and Parkinson's disease—conditions associated with loss of olfactory function (Jagust and Eberling, 1991; Jolles et al., 1989).

III. BASIC ANATOMY AND PHYSIOLOGY OF THE OLFACTORY SYSTEM

Since the anatomy and physiology of the olfactory system is discussed elsewhere in this volume (see Chapters 1–9), we only briefly mention this topic here. The sensation of smell is induced by the stimulation of olfactory receptor cells by volatile chemicals. The olfactory receptor cells, i.e., the primary olfactory neurons, are encompassed in the neuroepithelium, which is located at the top of the nasal vault, the upper portion of the nasal septum, the superior surface of the superior nasal turbinate, sectors of the middle turbinate, and the region of the cribriform plate. Afferent information from the receptors is transmitted by the olfactory nerves, which course through the cribriform plate of the ethmoid bone to terminate in the glomeruli of the olfactory bulb. In the olfactory bulb, the olfactory nerves make synaptic contact with dendrites of mitral and tufted cells. From there, the efferent neurons of the olfactory bulb give rise to fibers forming the olfactory tracts, which lie just under the gyrus rectus region in the olfactory sulcus of the frontal lobes. Axons from mitral and tufted cells project to central brain limbic system components including the pyriform cortex and adjacent corticomedial amygdala (which together form the uncus), the ventral striatum, the parahippocampus area, and the anterior olfactory nuclei. From these areas there are widespread interconnections with many parts of the brain, including the mediodorsal thalamus, hypothalamus, orbitofrontal and dorsolateral frontal cortex, temporal cortex, and other areas of the limbic system (see Chapters 8 and 9).

IV. PERIPHERAL CAUSES OF OLFACTORY DISTURBANCE

Sinonasal tract disease is one of the common causes of olfactory disturbance (Deems et al., 1991; Doty and Mishra, 2001). The etiology of the olfactory deficits among patients with nasal and paranasal sinus disease is due, in many cases, to nasal airway obstruction. The influence of nasal obstruction on olfaction has been comprehensively reviewed (e.g., Doty and Frye, 1989; Doty and Mirshra, 2001) (see also Chapter 21). Any cause of bilateral obstruction can decrease smell sensations by limiting airflow to the olfactory receptors. Besides the obstructive effect, lesions located in the upper nasal vault and/or cribriform plate region may also directly damage the olfactory epithelium and olfactory neurons (Kern, 2000). The common peripheral sinonasal tract causes of olfactory deficits include infections, tumors, allergic rhinosinusitis, congenital or developmental abnormalities, etc.

A. Sinonasal Infectious Disease

Paranasal sinusitis is a relatively common disorder affecting approximately 30% of the population at some time in their lives (Allphin et al., 1991). One of the common symptoms of acute and chronic paranasal sinusitis is decreased smell sensation, which is generally reversible. The prompt diagnosis and treatment of sinusitis are important for restoring olfactory function. Though the exact cause of chemosensory dysfunction secondary to sinusitis is elusive, alterations in nasal air flow and mucociliary clearance or obstruction from secretory products, polyps, or retention cysts may contribute to olfactory dysfunction (Loury and Kennedy, 1991).

In the diagnosis and evaluation of paranasal sinusitis, medical imaging plays an important role. At present, high-resolution CT is the preferred imaging technique, preceded by nasal endoscopic examination. Radiographic manifestations of sinusitis have been well documented. In general, air-fluid levels are usually indicative of acute sinusitis, whereas mucoperiosteal thickening or sinus opacification can be seen in acute and chronic disease. Polyps, mucous retention cysts, sinus expansion, and bony thickening of the walls of the sinus might also indicate chronicity of disease. CT is an excellent modality for the evaluation of bony abnormalities, such as osteitis or remodeling, seen in some inflammatory lesions. CT also will identify the infundibulum, the maxillary sinus ostium, the middle meatus, the uncinate process, and the individual ethmoid air cells that make up the ostiomeatal complex. This will help the functional endoscopic sinus surgeon in his ability to plan effective surgery to restore normal mucociliary clearance. On the other hand, MRI is also highly sensitive for detecting mucosal thickening and other soft tissue abnormalities (Shapiro and Som, 1989). By and large, inflamed mucosa is usually high in signal intensity on T_2-weighted MR images and low in intensity on T_1-weighted scans. The signal intensity of the sinus secretions will vary with the concentration of protein within the sinus (Barat, 1990; Drutman et al. 1991; Shapiro and Som, 1989).

B. Tumors of the Nasal Cavity and Paranasal Sinuses

Neoplasms of the sinonasal tract are uncommon. Malignant tumors of the nasal cavity and paranasal sinuses account for

only 0.2–0.8% of all human malignancies (Som, 1991). Early symptoms of sinonasal tract tumors, such as nasal discharge, unilateral nasal obstruction, and minor intermittent epistaxis, may simulate low-grade chronic infection. Subsequent symptoms depend on the tumor's location and pattern of growth. Neoplasms arising in the upper nasal cavity and extending through the cribriform plate or into the ethmoid sinuses are often accompanied by frontal headache, visual disturbances, and decreased smell sensation. Almost all sinonasal tract tumors and tumor-like conditions that grow to a large size may cause a decline in olfactory acuity by interfering with patency of the nasal airway or directly destroying the olfactory receptors. The most common malignancies of the sinonasal system are squamous cell carcinoma and adenocarcinoma, but lymphoma, melanoma, adenoid cystic carcinoma, and chondrosarcomas also populate the nasal cavity. Two examples of intrinsic sinonasal tract tumors relatively unique to the sinuses (the olfactory neuroblastoma and the inverted papilloma, both of which often cause hyposmia or anosmia) may serve as prototypes for masses in this region.

1. Olfactory Neuroblastoma

Olfactory neuroblastoma, or esthesioneuroblastoma, is a rare nasal tumor originating from the olfactory neuroepithelium lining the roof of the nasal vault and in close proximity to the cribriform plate. There have been less than 300 reported cases in the world literature. Olfactory neuroblastomas occur in all age groups with a peak incidence in the 11–20 and 51–60 year groups. There is a slight preponderance of the tumor in women. The incidence of olfactory neuroblastoma has been estimated to range from 2 to 3% of all malignant intranasal neoplasms. The most common symptoms are unilateral nasal obstruction and recurrent epistaxis. Hyposmia or rhinorrhea is not unusual. Extension into the orbit, paranasal sinuses, or anterior cranial fossa may cause vision disturbances and headache (Elkon et al., 1979; Li et al., 1993; Newhill et al., 1985). In the detection and staging of olfactory neuroblastoma, CT and/or MRI play an important role. Generally speaking, MRI is more accurate than CT in showing the tumor's intracranial extent. MRI is also exquisitely useful for differentiating neoplasm from *postobstructed* secretions because of the difference in the signal intensity (secretions are bright on T_2, tumor intermediate). Unfortunately, signal intensity characteristics of various sinonasal tract tumors overlap each other, so MRI cannot usually predict specific tumor histology. However juvenile angiofibroma can usually be distinguished from other tumors on the basis of its high vascularity and marked enhancement.

A recently described imaging finding characteristic of olfactory neuroblastomas is the presence of peripheral peritumoral cysts along the intracranial portion of the tumor. If stippled calcifications are also seen on CT, the diagnosis is assured.

2. Inverted Papillomas and Other Sinonasal Tumors

The inverted papilloma is a relatively rare and locally aggressive sinonasal tumor. It constitutes 0.5–4% of primary nasal tumors and occurs predominantly in males in the fifth and sixth decades of life (Phillips et al., 1990). The most common presenting symptoms are nasal obstruction, epistaxis, and hyposmia. Subsequent sinusitis and tumor extension into the sinuses and orbits can cause purulent nasal discharge, pain, and diplopia (Som, 1991). Radiographic findings of inverted papilloma can vary from a small nasal polypoid nodule to an expansile large mass, which may remodel the nasal vault and extend into the sinuses, orbits, or even the anterior skull base. CT and MRI are very useful in defining the location and extension of the tumor (Buchwald et al., 1990; Yousem et al., 1992) (Fig. 1.). Calcification is not uncommon in this tumor.

Other sinonasal tract tumors, such as squamous cell carcinoma, adenocarcinoma, melanoma, etc., can also cause hyposmia or anosmia during their late stage. Squamous cell carcinoma accounts for 80% of paranasal sinus malignances, is most commonly seen in the maxillary sinus, and usually demonstrates bone destruction at the time of presentation. Adenocarcinomas occur most frequently in the ethmoid sinus while melanoma is usually seen intranasally.

Additional benign neoplasms known to affect the sinonasal cavity include osteomas, enchondromas, schwannomas, and juvenile angiofibromas. Osteomas are usually identified in the frontal sinus and may be a source for recurrent headache and/or recurrent sinusitis. The classic story of a frontal sinus osteoma narrowing the sinus opening is a patient who has severe sinus pain associated with takeoffs from airplane flights. This is a benign mass, which is often completely invisible on MRI due to the presence of dense compact bone making up the mass. On the other hand, it is easily identified on CT as a markedly hyperdense bony mass protruding in the sinus. Occasionally, the osteoma will result in mucocele formation and/or pneumocephalus as the posterior wall of the frontal sinus is breached.

Enchondromas are less common neoplasms of the sinonasal cavity which, on CT, often have a popcorn calcification appearance different from the stippled calcification of inverted papillomas. This lesion, because of its characteristic calcification, is best evaluated with CT.

Schwannomas of the fifth cranial nerve are the most common to affect the sinonasal cavity. They will typically

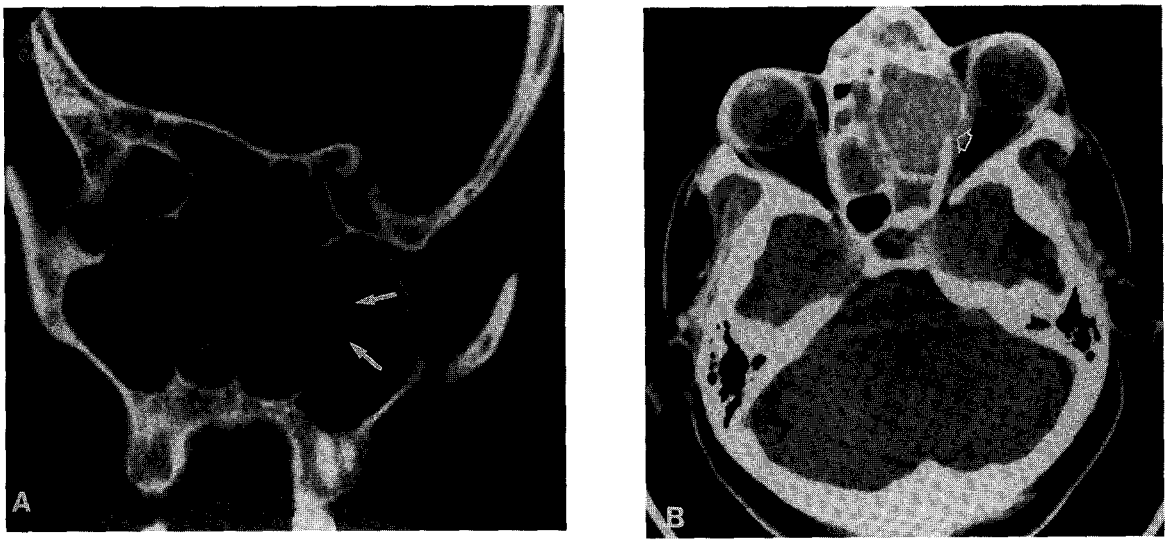

Figure 1 A 40-year-old woman with 3-month history of decreasing smell sensation and left nasal obstruction. (A) Bone-targeted coronal CT shows an expanded opacified left nasal cavity with bowing of the lateral nasal wall (arrows) and opacification of the left maxillary and both sphenoid sinuses. (B) Axial contrast-enhanced CT scan shows erosion through the left lamina papyracea (arrow) with displacement of the medial rectus and globe laterally. The differentation between tumor and obstructed secretions is not readily apparent with CT. Histological diagnosis: nasal cavity carcinoma arising within a dysplastic inverted papilloma.

follow the course of the nerve and can expand skull base foramina through which they travel. The signal intensity of schwannomas varies according to the content of the dense Antoni A tissue or loose Antoni B tissue, the latter being brighter on T_2W scans. Schwannomas enhance avidly, although they may have inhomogeneity to the enhancement.

Finally, one has the juvenile angiofibroma, a fascinating benign neoplasm, which appears to arise in the region of the sphenopalatine foramen and/or the pterygopalatine fossa The lesion accounts for 0.5% of head and neck masses and is typically seen in adolescent males who present with epistaxis and/or a nasal mass (Mehra, 1989). The lesion is highly vascular as exemplified on MRI by the signal flow voids within the lesion and its marked contrast enhancement. Because of its propensity for spreading via the canals and foramina at the skull base, MRI is probably the study of choice for the evaluation of this neoplasm. Embolization of these lesions will assist the surgeon in limiting blood loss if resection is considered.

3. Malignant Neoplasms

CT and MRI probably play complementary roles in the evaluation of sinonasal malignancies because of CT's superiority in defining bony margins and MRI's superior soft tissue resolution and ability to define intracranial or intraorbital spread. One of the advantages of MRI is the ability to distinguish sinus neoplasm from postobstructive secretions. This may be difficult by CT if the secretions are isodense to the mass and if the malignancy does not enhance dramatically. If one was forced to study the patient with a single modality, the literature supports MRI as the best study for the staging of sinonasal malignancies (Hunink et al., 1990; Kraus et al., 1992; Paling et al., 1987; Sisson et al., 1989).

Som et al. (1991) noted that squamous cell carcinoma (low in T2 intensity) could be distinguished from inflammation (high in T2 intensity). They compared CT to MRI for mapping sinonasal tumors. They found that MRI and CT were equivalent in 23 of 53 patients in defining tumor extent and that MRI was superior to CT in 26 patients. Of the 4 cases in which CT was superior, subtle bony erosion (2) and osteo(1)-cartilaginous(1) lesions accounted for the "misses" on MRI. Of 60 inflammatory lesions, MRI was superior (Bonte et al., 1993) or equivalent (Everall et al., 1991) to CT in all cases. Inflammation (bright) and neoplasm (intermediate) could be distinguished in 95% of cases based on T_2W signal intensity. Even when the sinus secretions become increasingly inspissated and the signal intensity on T_2W scans decreases, the neoplasm can be distinguished from the obstructed secretions by its typical heterogeneity as opposed to the smooth homogenous

appearance of sinus secretions. This is also true in the cases of mucoceles, which may occur after or in association with sinus neoplasms. Additionally, MRI has shown that most squamous cell carcinomas of the sinonasal cavity enhance with gadolinium in a solid fashion as opposed to a peripheral rim of enhancement in sinus secretions and/or mucoceles. Unfortunately, lymphomas, undifferentiated carcinomas, inverted papillomas, and some sarcomas may have identical signal intensity and enhancement characteristics as squamous cell carcinoma.

Gadolinium is particularly useful for demonstrating epidural or meningeal invasion of neoplasms. Often, postcontrast scans must be combined with fat suppression techniques in order to identify enhancement amidst the abundant skull base fat. In one series, 75% of patients with intracranial extension of sinonasal malignancies had additional information about tumor extent demonstrated with postcontrast MRI studies (van Tassel et al., 1991). Subtraction MRI of pregadolinium scans from postgadolinium scans may improve visibility of such subtle enhancement (Lloyd and Barker, 1991). It should be noted that meningeal enhancement need not necessarily imply neoplastic invasion; just as in cases of meningioma, the dura may enhance because of reactive fibrovascular changes alone.

When one encounters a sinonasal mass that is eroding intracranially, one must consider carcinoma, olfactory neuroblastoma, sarcomas, lymphomas, sinonasal polyposis, and inverted papillomas. Twelve percent of patients with polyposis and mucoceles eventually erode the skull base (Som et al., 1991). The pattern of bone destruction may be similar between malignant and benign lesions at the non–sinus bearing skull base. Bone remodeling in this location is a rarity; a permeative pattern is the norm for all lesions. Som et al. (1988) have suggested that a lesion with homogeneous signal intensity invading intracranially is more likely to be a malignancy, whereas heterogeneity suggests an inflammatory cause. Unfortunately, necrosis, hemorrhage, or calcification in carcinomas, olfactory neuroblastomas, or sarcomas may cause signal heterogeneity. Polyps generally enhance in a peripheral pattern; true neoplasms enhance solidly. Malignancies have a broad flat base of skull erosion; benign conditions have a rounded polypoid intracranial excrescence.

Squamous cell carcinomas account for 80% of the malignancies to affect the paranasal sinuses and 80% in the maxillary sinus. The hallmark of malignancies of the sinonasal cavity is bony destruction, seen in approximately 80% of CT scans of sinonasal squamous cells carcinoma at initial presentation. The lesion is confined to the maxillary antrum in only 25% of cases at presentation (Lyons and Donald, 1991). In most series documenting sinonasal squamous cell carcinoma signal intensity characteristics on MRI, the lesion is characterized by a low signal intensity on T_2W scans. This is why differentiation with obstructed secretions which are typically bright in signal intensity on T_2W scans is so easy on MRI.

Because of Som et al.'s early work depicting sinonasal malignancies as hypointense on T_2W scans, people have come to rely on this pulse sequence for mapping cancers (Som et al., 1990). Unfortunately, low intensity on T_2W scans is an inconstant finding in sinonasal malignancies in general. Hunick et al. found that over 50% of head and neck malignancies had signal intensity on T_2W scans that was brighter than muscle and isointense to brain (Hunink et al., 1990). Approximately 25% of benign tumors had the same intensity pattern. Lanzieri et al. (1991) also reported that the signal intensities of tumors, mucoceles, schwannomas, and obstructed secretions may show some overlap. Som et al. (1991) have found that minor salivary gland masses and schwannomas may have T_2W signal intensity similar to that of inflammatory lesions. Minor salivary gland tumors and melanoma are the next most common malignancies to affect the sinonasal cavity after squamous cell carcinoma (van Tassel et al., 1991). The minor salivary gland tumors represent a wide variety of histological types including adenoid cystic carcinoma, mucoepidermoid carcinoma, adenocarcinoma, and undifferentiated carcinoma. Of these tumors, adenoid cystic carcinoma is the most common variety. Its signal intensity may be high or low on T_2W scans, possibly related to the degree of tubular or cribriform histological pattern as well as cystic spaces, necrosis, and tumor cell density. Tissue specificity is not readily achievable with MRI or CT. Gadolinium is of particular use with adenoid cystic carcinomas, which have a propensity for perineural spread (Graamans and Slootweg, 1989). With sinonasal cavity malignancies one should always attempt to trace back the branches of the fifth cranial nerve via the pterygopalatine fossa, foramen rotundum, foramen ovale, and orbital fissures in order to identify perineural neoplastic spread.

Adenocarcinomas of the paranasal sinuses have a predilection for the ethmoid sinuses and appear more commonly in woodworkers. This tumor also tends to have low signal intensity on T_2W MRI images but may have high signal intensity in a small percentage of cases.

Sarcomas of the sinonasal cavities are very rare, with chondrosarcoma being the most common. Again, the histological diagnosis is probably better suggested by CT based on the characteristic whorls of calcification. However, for staging, MRI is competitive with CT, and, particularly if repeat examinations are going to be required, follow-up with MRI to avoid the radiation exposure of CT is recommended.

Melanoma is a tumor that is usually identified in the nasal cavity as opposed to the paranasal sinuses. It has been associated with melanosis in which there is field deposition of melanin along the mucosal surface of the sinonasal cavity. Therefore, multiplicity of lesions becomes a problem when dealing with melanomas. Neither CT nor MRI is particularly helpful in identifying the field "cancerization" of melanoma. When melanoma contains melanin there is paramagnetism which causes T_1 and T_2 shortening accounting for high signal intensity on T_1W scans and low signal intensity on T_2W scans (Atlas et al., 1990). However, an amelanotic melanoma may have bright signal intensity on T_2W scans. The presence of hemorrhage associated with the melanoma, a common occurrence because of the coincidence of epistaxis, may further obfuscate the signal intensity pattern (Yousem et al., 1996c).

Lymphoma does occur in the paranasal sinuses and may have variable signal intensity as well. It is characterized by homogeneous signal intensity without necrosis and the association with cervical lymphadenopathy.

Metastatic disease to the paranasal sinuses is extremely rare. Of the primary causes of metastases to the sinuses, renal cell carcinoma is probably the most common. This tumor also has a propensity for hemorrhage and may also have a variable signal intensity depending upon the stage of hemorrhage.

C. Allergic Reactions

Allergic rhinitis is a common upper airway condition affecting about 30 million Americans with peak prevalence in the age group from 35–54 years (Baroody and Naclerio, 1991). Hyposmia or anosmia is common with allergic rhinitis, mainly caused by nasal obstruction by polyps or inflamed mucosa, which limit access of inspired air to the roof of the nasal vault (Cowart et al., 1993). The diagnostic work-up begins with a careful history, which attempts to identify offending allergens. Skin testing of specific antigens is often used to confirm the diagnosis. Medical imaging studies play a supplementary role in the evaluation of sinonasal airway status and differential diagnosis. CT and MRI are also important for detecting any complications such as sinusitis, mucoceles, and aggressive polyps in patients with allergic rhinitis. Rounded excrescences and enlargement of ostia are seen in the airway of patients with polyposis.

D. Congenital or Developmental Abnormalities

It is generally accepted that normal variations in the nasal anatomy may play a role in preventing the access of an odorant to the olfactory receptor area. The sense of smell is probably less than normal in many patients with craniofacial anomalies (Crysdale, 1981). Congenital developmental abnormalities include choanal atresia, hereditary nasal septal deviation, facial hypoplasia, cleft palate, nasal dermoids and epidermoids, cephaloceles, and gliomas, etc. Medical imaging techniques, especially high-resolution CT, play a key role to detect and evaluate the facial and bony changes (Barkovich et al., 1991; Klein et al., 1987). CT is most useful because surgical correction requires identification of and closure of the osseous abnormalities. MRI is most effective in defining soft tissue masses such as cephaloceles and nasal gliomas.

Congenital anosmia can be associated with a number of developmental and inflammatory conditions. Kallmann's syndrome, also known as hypogonadotrophic hypogonadism with anosmia, is a congenital X-linked disorder in which the olfactory bulbs and tracts are not formed. This is not associated with holoprosencephaly, and the usual deficits are related to hormonal abnormalities in the pituitary gland with the loss of sense of smell. Infertility often coexists. In 1993, an MR study of the olfactory system in Kallmann's disease showed absence of the olfactory bulbs and tracts in 17 of 18 patients while confirming the presence of the olfactory bulbs and tracts in all 10 studied patients with idiopathic hypogonadotropic hypogonadism (Yousem et al., 1993, 1996a). Some patients have absence of the olfactory bulbs and tracts without Kallmann's syndrome. It is unclear whether this represents congenital absence or whether an inflammatory condition early in infancy destroys the olfactory bulbs and tracts. Certain viruses have a propensity for injuring the olfactory system. A recent study has noted the incomplete formation of olfactory sulci in patients with congenital anosmia as well as a variable percentage of aplastic olfactory bulbs, tracts, and tubercles (Di Rienzo et al., 2002). Still others may have congenital absence of sense of smell on the basis of early head trauma where the ciliary nerves as they crossed the cribiform plate may be sheared and the olfactory system is affected. Infectious causes may also affect the sense of smell in early childhood, usually secondarily to viruses. In these cases one sees the olfactory bulbs and tracts; but they are not functional.

Holoprosencephaly is a congenital, multiple midline malformation disorder that has a known association with sensory deficits of vision and olfaction. Although variable amounts of aplasia and hypoplasia of the olfactory apparatus may be identified, the most common MR finding is complete absence of the olfactory bulbs, occurring in 92% of patients. A high association with absence of the olfactory nerves and tubercles is also seen. There does appear to be some, albeit poor, differentiation of the olfactory sulci and gyri recti, which were absent only in a little over half of the subjects (Barkovich and Quint, 1993).

E. Other Peripheral Causes

It is estimated that 30 million Americans have used cocaine and 5 million use it regularly (Gregler and Mark, 1986). Intranasal use of cocaine and heroin has reached epidemic proportions in the United States. Although hyposmia or anosmia has been suggested to occur often in cocaine abusers, few studies using quantitative measures of olfactory function have confirmed such reports. A sole study on this topic reported that of 11 cocaine abusers who underwent detailed olfactory testing, only one was found to be anosmic and another had mild olfactory discrimination dysfunction (Gordon et al., 1990). These authors note that most cocaine abusers do not develop permanent olfactory dysfunction. If, in fact, olfactory disturbance occurs as a result of heavy cocaine use, it could be due to associated conductive disorders, nasal airway obstruction, alteration in sinonasal aerodynamics, damage to the olfactory epithelium, damage to the central olfactory system, or osteolysis of the cribriform plate (Kuriloff, 1989).

Concerning the conductive disorders, several reports of osteolytic sinusitis and extensive osteocartilaginous necrosis of the nasal septum in cocaine abusers have been described (Newman, 1988; Schweitzer, 1986). Erosion of nasal septal cartilage is a known complication of cocaine abuse. Within the differential diagnosis for cartilaginous destruction, one should include Wegener's granulomatosis, syphilis, leprosy, lymphoma, rhinoscleroma (a klebsiella infection), and fungal invasion. CT, preferably in the coronal plane, can provide excellent views of septal perforation, osteolysis, and sinusitis.

To evaluate intracranial disorders associated with cocaine, MRI is the study of choice. Vasculitic infarcts, hypertensive hemorrhages, and white matter ischemic foci may be seen with MRI. Recently Tumeth and colleagues demonstrated multifocal cortical deficits with a special predilection for the frontal and temporal lobes on SPECT perfusion brain scans in chronic cocaine abusers (Tumeth et al., 1990). Similar findings have been reported by others (Holman et al., 1991; Kolow et al., 1988). These findings may suggest a central basis for some cases of cocaine-related decreased olfaction. Some studies also have revealed that cerebral atrophy develops in chronic cocaine abusers and that the severity correlates with the duration of abuse (Pascual-Leone et al., 1991).

Anosmia or hyposmia is a frequent sequela of high-level midface fractures in which the olfactory nerves may be severed at the level of the cribriform plate (Kassel, 1988; Mathog, 1992). Because ethmoid complex and cribriform plate fractures are difficult to detect on plain radiographs, thin-section coronal CT is the best measure to assess naso-ethmoid trauma (Daly et al., 1990; Kassel, 1988).

V. CENTRAL CAUSES OF OLFACTORY DISEASES

There are numerous CNS disorders that are associated with olfactory dysfunction. The most common types fall in the categories of degenerative neuropsychiatric disorders, hereditary conditions, trauma, and central neoplasms. Of course, in some disorders the involvement of both peripheral and central neural processes may occur.

A. Alzheimer's Disease

It has been well documented that olfaction is significantly altered in Alzheimer's (AD). Nearly all studies of olfactory function in patients with AD have reported decreased smell relative to age-matched controls (see Chapter 23). These studies demonstrate marked impairment of smell function in early AD, whether measured by identification, discrimination, or threshold sensitivity (Doty, 1991; Doty et al., 1987; Serby et al., 1991).

Recent neuropathological studies have correlated well with these clinical findings. The anterior olfactory nuclei in AD patients contain senile plaques, neurofibrillary tangles, granulovascular degeneration, and cell loss (Averback, 1983; Esiri and Wilcock, 1984). The olfactory bulbs also show involvement (Esiri and Wilcock, 1984; Ohm and Braak, 1987), as does nasal sensory epithelium (Jafek et al., 1992). In addition, central olfactory structures, especially the amygdala and the entorhinal, pyriform, and temporal cortices, are frequently affected by Alzheimer's disease (Harrison, 1986; Pearson and Powell, 1989). Besides the above findings, devastating nerve cell loss and gliosis in the region of the hippocampal formation have been observed at autopsy in AD patients (Ball et al., 1985; Hyman et al., 1984).

Neuroimaging has played an important role in detecting some of the pathological changes of AD patients in vivo, and its uses are growing, both for clinical evaluation and as a research tool. Early CT studies in AD patients demonstrated generalized enlargement of the ventricular system and sulci (George et al, 1981; Naser et al., 1980). Several reports have noted that ventricular and sulcal enlargement correlate with the severity of AD (Albert et al., 1984; George et al., 1983). However, these findings are not specific and have relatively weak correlations. de Leon and colleagues (1989) have emphasized the rate of change in ventricular size with repeated CT scans as an important index in the diagnosis of AD. Recently, several investigators have recog-

nized that CT and/or MRI delineation of atrophic changes in the temporal lobe and the hippocampus with enlargement of hippocampal-choroidal fissures strongly support the diagnosis of AD (de Leon et al., 1988; George et al., 1990; Kesslak et al., 1991; Kido et al., 1989).

McDonald and colleagues (1991) reviewed MRI scans in 22 patients with early-onset AD. The results showed that patients with AD were significantly more likely than age-matched controls to have MR evidence of periventricular hyperintensities on T_2W scans. This study suggested that the increased frequency of periventricular hyperintensities may have a relationship to the disease process. Our own experience with MRI studies of AD patients is that most of the cases with AD have, in addition to ventriculomegaly and sulcal widening, significantly reduced volume of the temporal lobe and slight atrophy of olfactory bulbs. (Fig. 2).

Besides CT and MRI, SPECT and PET techniques are also useful for evaluating regional cerebral blood flow, regional oxygen, and glucose metabolism, which may provide evidence supportive of the diagnosis of AD (Jagust and Eberling, 1991). The above-mentioned structural atrophic changes by CT and MRI are also supported by functional imaging studies (McDonald et al., 1991; Ohnishi et al., 1991). The major findings of functioning imaging studies in patients with AD are abnormal regional cerebral blood flow pattern and flow reduction. The common sites of blood flow reduction are in the temporoparietal region and the frontal areas. In one report (Bonte et al, 1993), seven patients with possible diagnosis of AD studied by SPECT showed only frontal flow abnormalities. Is this an early imaging finding which may suggest a pathophysiologic basis to explain the decreasing smell sensation in AD? Of course, more studies are needed for further discovering the nature of AD. We believe that early and correct diagnosis of AD in vivo by neuroimaging techniques will be possible in the near future.

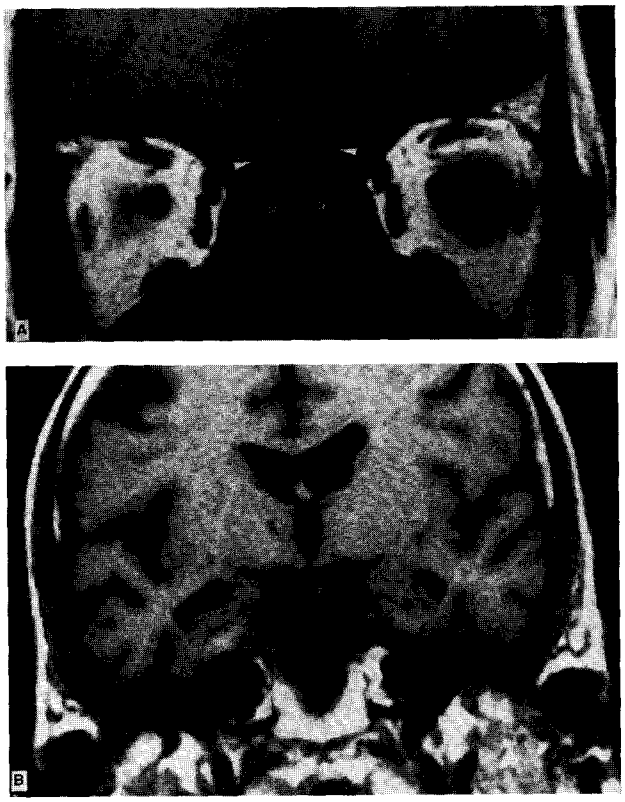

Figure 2 A 60-year-old woman with Alzheimer's disease. UPSIT scores revealed severe bilateral anosmia. (A) Normal olfactory bulbs are seen (arrows) on coronal MR. Dilation of the olfactory sulci (arrowheads) reflects generalized atrophy. (B) Coronal MR scan through the temporal lobes shows temporal horn enlargement and atrophic changes, slightly worse on the right side.

There is a dose-related association between apolipoprotein E-4 (APOE-4) allelic frequency and the development of AD (APOE-2 may confer protection). Recent studies have shown a decline in resting parietal, temporal, and prefrontal PET glucose metabolism in cognitively intact patients with APOE-4. It remains to be seen whether this, and/or an analogous fMRI study, may serve to be a predictor of development of AD.

Recently some investigators have used dynamic contrast susceptibility contrast imaging MR to try to duplicate the nuclear medicine flow studies. Indeed they have found that relative values of temporoparietal regional cerebral blood volume (as a percentage of cerebellar rCBV) were reduced by a factor of 20% bilaterally in the patients with Alzheimer disease compared to normals. Using left and right temporoparietal rCBV as index measures, specificity was 96% and sensitivity was 95% in moderately AD and 88% in mild AD (Harris, 1998).

B. Parkinson's Disease

Odor detection and identification are significantly impaired in Parkinson's disease (PD) patients (Doty et al., 1988, 1995; Montgomery et al., 2000) (see Chapter 23). It is unclear whether the olfactory deficits in PD and AD share the same cause. Not surprisingly, PD research into the cause of smell dysfunction has focused on dopaminergic changes. Brooks and colleagues (1991) have demonstrated by using PET that patients with PD show significantly reduced mean uptake of 18F-dopa in the caudate and putamen, especially in the posterior part of the putamen. Previous functional imaging studies have also indicated a reduction of striatal dopamine storage in PD.

PET technique with 18F-dopa in PD patients has also demonstrated reduced basal ganglia activity (Alavi and Hirsch, 1991). However, the olfactory deficit is unrelated to severity of motor or cognitive symptoms and is not improved by L-dopa therapy (Doty et al., 1992), so the underlying causes of olfactory dysfunction in PD still requires more study.

CT scanning has little role in establishing the diagnosis of PD other than to exclude mass lesions in the brain. In general, CT shows no specific striatal abnormalities and occasionally only mild, nonspecific ventricular and sulcal enlargement. The major feature of PD on MRI appears to be a trend towards a decreased width of the pars compacta of the substantia nigra (Braffman et al, 1989). There is a lateral to medial gradient of loss of the normal signal of the pars compacta as well as volume loss. Moderate or marked cortical atrophy tends to occur more frequently in PD patients than in controls. MRI may occasionally show abnormal decreased T_2W intensity in the putamen and to a lesser degree in the caudate nuclei and substantia nigra, suggestive of iron deposition (Drayer et al, 1986).

C. Huntington's Disease

Patients with Huntington's disease (HD) evidence olfactory dysfunction (Doty, 1991; Moberg et al., 1987). Neuropathological studies in HD have demonstrated premature neuronal cell death and reactive gliosis occurring most markedly in the head of the caudate nuclei bilaterally (Myers et al., 1991; Vonsattel et al., 1985). A loss of 70–80% of the striatal neurons may occur before functional impairment is obvious. Similar but less extensive changes also affect the putamen. Later, atrophy of the cerebral cortex occurs as well. All of these progressive atrophic changes can be identified on CT and MRI scans, especially in the caudate nuclei, where the volume of the caudate head decreases and the intercaudate distance increases (Simmons et al., 1986; Starkstein et al., 1989). Increased signal intensity in the putamen and globus pallidus has been described in the juvenile form of Huntington's disease, and frontal atrophy is usually present.

PET studies of patients with HD have consistently demonstrated hypometabolism in the caudate nuclei, often before the development of atrophy on CT (Hayden et al., 1986). SPECT studies involving HD patients have also revealed decreased uptake in the caudate nuclei, including the caudates of one patient with early disease and no evidence of atrophy on MRI (Nagel et al., 1988; Reid et al., 1988). Thus, functional imaging with PET or SPECT may contribute to the early diagnosis of HD.

Theoretically, the input of caudate/putaminal fibers to the limbic system and striatum may be altered, leading to olfactory dysfunction, but the exact mechanism for hyposmia in HD patients remains to be worked out.

D. Korsakoff's Psychosis

Patients with Korsakoff's psychosis (KP) exhibit impaired odor detection, identification, and intensity estimation (Jones et al., 1975; Mair et al., 1986). An animal model study has shown that the behavior of rats recovering from pyrithiamine-induced thiamine deficiency share several important features with KP patients, including the impairments observed for smell, hearing, learning, and memory (Mair et al., 1991). The mechanism of hyposia and/or dysosmia in patients with KP is unclear and still under investigation. Olfactory perception may be selectively impaired in KP by the diencephalon lesions that are characteristic of this disease. Degeneration in the mediodorsal thalamic nucleus (the common neuropathological lesion in KP) and atrophy in the prefrontal areas may also cause the olfactory dysfunction (Mair et al., 1986).

A quantitative neuropathological study of the human cerebral cortex has shown that the number of cortical neurons in the superior frontal lobe in chronic alcoholic patients is significantly reduced (Happer et al., 1987). Chronic alcoholism is also associated with smaller volumes of cortical white and gray matter relative to controls (Pfefferbaum et al., 1995). Traditional neuropsychological tests and functional imaging studies have also demonstrated disturbances of frontal-lobe function and metabolic deficits in patients with KP (Joyce and Robbins, 1991; Kopelman, 1991; Metter et al., 1989).

Brain CT scans have demonstrated that KP patients show more pronounced third and lateral ventricular dilatation and wider interhemispheric fissures than matched groups of normal controls and non-Korsakoff alcoholics (Jacobson and Lishman, 1990; Ron, 1983; Ron et al., 1982). Shrinkage in the frontal lobes and cerebellum appears to be especially pronounced (Jacobson and Lishman, 1990). A MRI study (Jernigan et al., 1991) has revealed that patients with KP show widespread reductions in gray matter volumes in addition to CSF increases, with the greatest reductions observed in diencephalic structures. The volume losses that best differentiate the KP patients from the alcoholic controls included losses in anterior portions of the diencephalon, mesial temporal lobe structures, and orbitofrontal cortices (areas involved in olfaction perception). Several other studies (Donnal et al., 1990; Gallucci et al., 1990; Squire et al., 1990; Victor, 1990) have also demonstrated that MRI is highly sensitive in detecting reversible diencephalon (medial thalamic) and mesencephalic (periaqueductal) lesions. In addition to generalized cortical and cerebellar vermian atrophy seen on CT

and MR, recent reports have noted the presence of high signal intensity areas in the periaqueductal gray matter of the midbrain (40%), the paraventricular thalamic regions (46%), the mamillothalamic tract, and in tissue surrounding the third ventricle on T_2W MR scans (T_2WI). Reversible thalamic lesions in the dorsal medial nuclei have also been reported. These areas may or may not enhance (in some cases the enhancement may be dramatic, almost sarcoid-like) and may be associated with mamillary body atrophy. Mamillary body enhancement may be the sole manifestation of Wernicke's encephalopathy. Myelin degeneration, mamillary body volume loss, intracellular edema, and microglial proliferation are seen pathologically (but may be present in alcoholics without Wernicke's).

MRI findings in patients with KP may enable early diagnosis of the disease, which may have a positive effect on both treatment and prognosis (Gallucci et al., 1990).

E. Schizophrenia

Impaired olfactory function has been reported in schizophrenics, especially males (see Chapters 23 and 24). These olfactory deficits, which are not of the same magnitude as those seen in AD and PD, are perhaps not unexpected given the occurrence of olfactory hallucinations as symptoms in a number of patients with schizophrenia and the evidence linking both to temporal lobe dysfunction (Rausch et al., 1977; Roberts, 1988). Neuropathological studies in schizophrenic patients have reported neuronal loss in the entorhinal region and prefrontal cortex, gliosis in the basal limbic structures of the forebrain, and atrophy in temporolimbic structures (Benes et al., 1986; Falkai et al., 1988). Neurophysiological function studies (including regional cerebral blood flow, brain electrical activity mapping, and regional metabolic activity in the brain) in patients with schizophrenia have demonstrated prefrontal cortex and temporal lobe dysfunction (Mesulam, 1990). Functional imaging, such as PET or SPECT, in the study of schizophrenia is limited and inconclusive. However, functional imaging has provided some evidence that certain schizophrenic patients have decreased blood flow and metabolism in the frontal lobes (hypofrontality) (Alavi and Hirsch, 1991).

Anatomical imaging findings have basically paralleled the neuropathological changes in the brains of patients with schizophrenia. The most consistent finding on both CT and MRI is an increase in the size of the cerebral ventricular system, especially in the frontal and temporal horns, and corresponding decreases in cerebral tissue, especially in the prefrontal cortex and in medial temporolimbic structures (Mesulam, 1990; Suddath et al., 1989; Young et al., 1991). Suddath and colleagues (1989) evaluated the volume of the temporal lobes in schizophrenias by a quantitative MRI study. The results showed that the volume of temporal lobe gray matter was 20% smaller in the patients than in the control subjects, and lateral ventricular volume was 67% larger in the schizophrenia group than in the control group. Schizophrenic patients tend to have smaller hippocampi that matched controls. schizophrenias are also reported to have cavum septum pellucidum more frequently than controls. In a recent study, Turetsky et al. (2000) reported that patients with schizophrenia exhibited 23% smaller olfactory bulb volume bilaterally than comparison subjects by a quantitative MRI study.

F. Congenital Anosmia

Congenital anosmia, which traditionally has been defined as anosmia present from a patient's earliest recollection, has been recognized for centuries. The most common form of congenital anosmia is Kallmann's syndrome or olfactory dysplasia, which is characterized by hypogonadotropic hypogonadism and anosmia (Kallmann et al., 1944; Lieblich et al., 1982). The incidence of Kallmann's syndrome is about 1:100,000 in men and 1:50,000 in women. There has been increasing interest in the pathology, pathophysiology, and genetics of this disorder. Pathological and surgical studies of patients with Kallmann's syndrome have shown agenesis of the olfactory bulbs (DeMorsier and Gauthier, 1963; Males et al., 1973). Laboratory findings include decreased serum follicle-stimulating hormone and luteinizing hormone as well as decreased urinary gonadotropins (Lieblich et al., 1982).

In medical imaging studies, CT is a limited tool for the demonstration of sinonasal and intracranial abnormalities in patients with congenital anosmia (Klein et al., 1987; Moorman et al., 1984). Surface coil MRI is the optimal modality to reveal the intricate details of the olfactory bulbs, tracts, and rhinencephalon in vivo. Klingmuller and colleagues (1987) have clearly demonstrated the olfactory sulci in a normal control group by MRI, but not in the patients with olfactory dysplasia. More recently, the authors have studied two cases with Kallmann's syndrome by MRI. Both showed no olfactory bulb at all and flattening of the gyrus recti (Yousem et al, 1993, 1996a); frontal and temporal lobe volumes were normal (Fig. 3).

In a mixed population of patents with congenital anosmia, we found olfactory bulb and tract absence (68–84%) and hypoplasia (16–32%) in all 25 cases studied. Eight individuals had Kallmann's syndrome (hypogonadotropic hypogonadism with anosmia). Temporal and/or frontal lobe volume loss were noted in 5 individuals, mild in all but one individual. We concluded that congenital anosmia

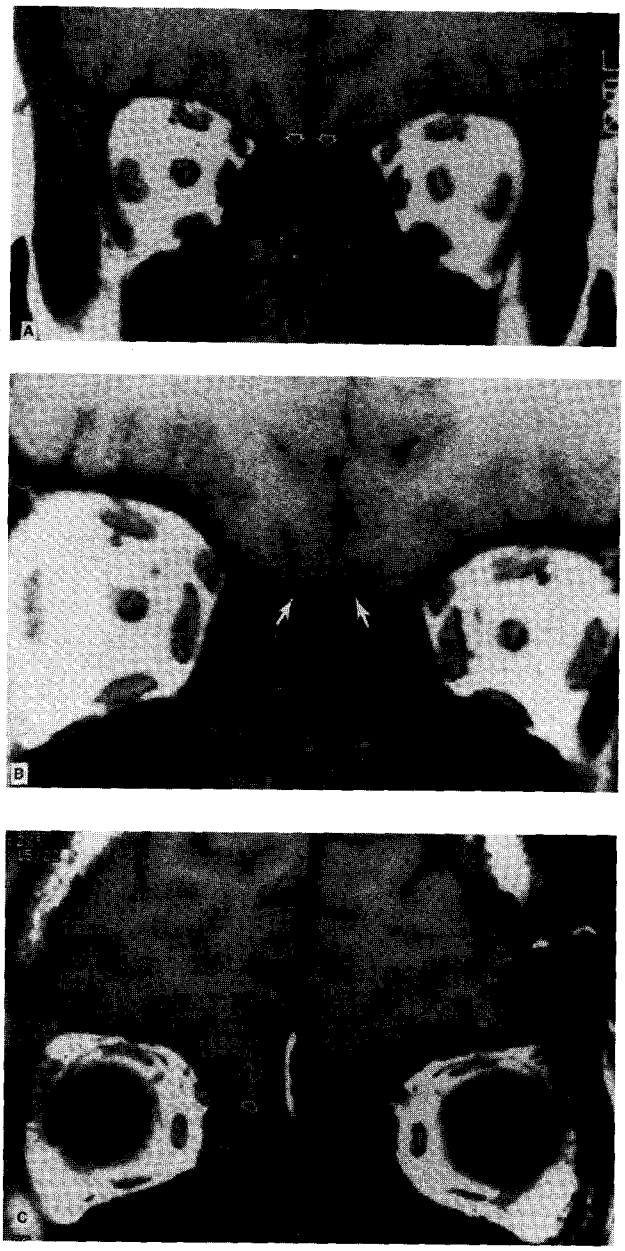

Figure 3 (A) Coronal 500/20 scan from normal volunteer (64-year-old woman with normal smell function) demonstrates normal olfactory bulbs (arrows). (B) Coronal 500/17 scan of 27-year-old woman with congenital anosmia without Kallmann's syndrome shows extremely atrophic olfactory bulbs (arrows). (C) Coronal 500/14 scan of 29-year-old male patient with Kallmann's syndrome evidences absence of olfactory bulbs and tracts with flattened gyrus rectus (arrow) on the right side, but with normal-appearing gyrus rectus on the left side.

or hyposmia appears to be an olfactory bulb tract phenomenon rather than a central process (Yousem et al., 1996a).

G. Head Trauma

Craniofacial trauma can alter olfactory ability through one of several mechanisms: (1) damage to the nose, sinuses, or both with resultant mechanical obstruction to odorants, (2) shearing of olfactory filaments as they course through the cribriform plate, (3) contusion to the olfactory bulb, and (4) contusion or shearing injury of the cerebral cortex, particularly the frontal and temporal lobes (see Chapter 30). The incidence of anosmia or hyposmia after head trauma has been reported quite variably from 2 to 38%, (Deems et al., 1991; Doty et al., 1997; Hagan, 1967; Leigh, 1943; Levin et al., 1985; Schechter and Henkin, 1974; Summer, 1964; Zusho, 1982) and increases with the severity of injury (Levin et al., 1985; Summer, 1964). However, even a minor injury can sometimes result in anosmia or hyposmia (Schechter and Henkin, 1974; Summer 1964). Recent evidence has shown that the location of the hematoma or contusion of the brain after head trauma is one of the most important factors leading to olfactory dysfunction (Costanzo and Zasler, 1991; Doty et al., 1997; Levin et al., 1985; Yousem et al., 1996b). Specifically, diminished olfactory discrimination has been confirmed in patients with prefrontal lesions (Potter and Butters, 1980). Animal studies have shown that the prefrontal olfactory area plays a prominent role in the fine and specific discrimination of odors (Tanabe et al., 1975). Besides prefrontal lesions, temporal lobe structures are also involved in the odor processing of odor perception (Rausch and Serafetinides, 1975; Rausch et al., 1977). Indeed frontal or temporal lobe hematomas or contusions are now believed to be one of the most common causes of olfactory dysfunction after head injury (Costanzo and Zaster, 1991; Doty et al., 1997; Levin et al., 1985; Schellinger et al., 1993; Yousem et al., 1996b) (Fig. 4).

It has been established that plain skull radiography plays only a small role in the evaluation of head trauma (Masters et al., 1987). CT currently is the study of choice when diagnostic imaging is necessary after acute head trauma (Cohen, 1990; Kelly et al., 1988). CT can detect subarachnoid hemorrhage, fractures, and intraventricular blood, lesions for which MRI is less sensitive acutely. CT can be performed with close patient monitoring in a rapid fashion. However, MRI is superior to CT in the detection and characterization of subacute injuries, hemorrhage outside the subarachnoid space as in subdural hematomas, cortical contusion, and shearing injuries. MRI is exquisitely sensitive to diffuse axonal injuries leading to demyelination. MRI is also useful in the follow-up of brain contusion and/or hemorrhage, thereby eliminating the radiation exposure associated with CT (Cohen, 1990; Zimmerman et al., 1986).

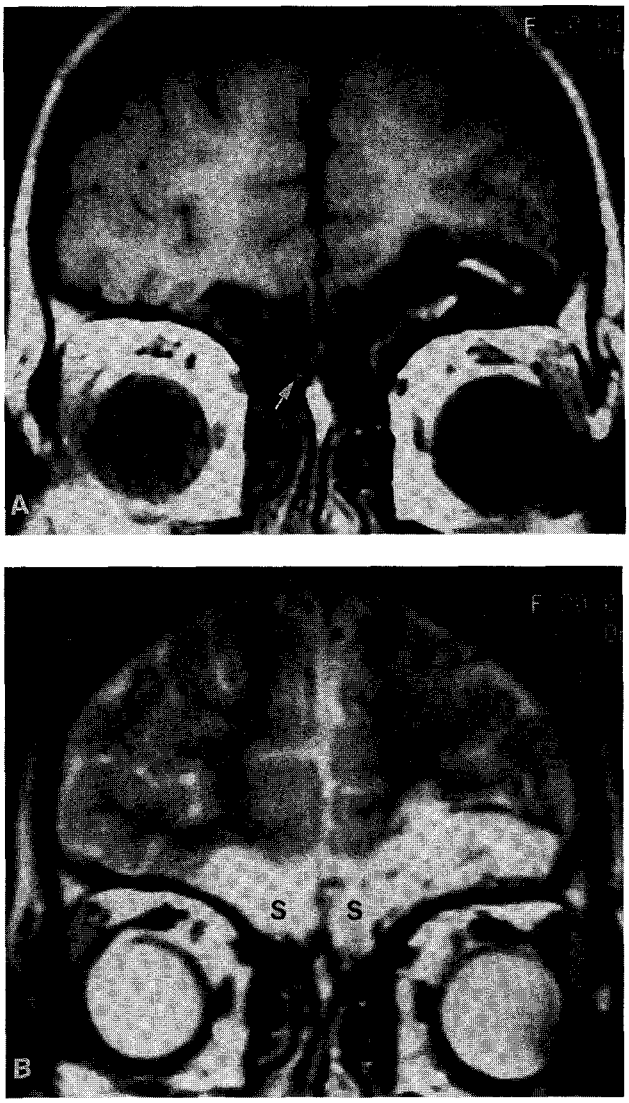

Figure 4 A 20-year-old woman with posttraumatic anosmia. (A) A small olfactory tract is seen on the right side (arrow), but none is seen on the left. Severe inferior frontal lobe encephalomalacia is soon on this coronal T_1W MR scan. (B) Encephalomalacia is well seen on the T_2W MR scan where hyperintense signal (S) has replaced the inferior frontal lobes (where smell processing occurs).

At at our institution, 25 patients with posttraumatic smell dysfunction were evaluated by olfactory testing and MR. Quantitative and qualitative gradings for olfactory bulb, tract, subfrontal region, hippocampus, and temporal lobe damage correlated with olfactory test results. Twelve patients were anosmic, 8 had severe impairment, and 5 were mildly or impaired. Olfactory bulb and tract (88% of patients), subfrontal (60%), and temporal lobe (32%) injuries were found but did not correlate well with olfactory test scores (Doty et al., 1997b; Yousem et al., 1996b). Abnormalities on MR in patients with posttraumatic olfactory dysfunction occur at a very high rate (88%), predominantly in the olfactory bulbs, tracts, and inferior frontal lobes. Qualitative and quantitative assessments of damage show little correlation with olfactory tests probably due to multifocal injury, ciliary nerve damage, and the constraints of small sample size.

H. Brain Tumors

The incidence of chemosensory changes caused by intracranial tumors has rarely been investigated. In a study of 750 consecutive patients presenting with chemosensory disorders to the University of Pennsylvania Smell and Taste Center, only two cases (0.3%) were induced by brain tumors (Deems et al., 1991). In one study anosmia was reportedly present in 19 of the 26 cases of Foster-Kennedy syndrome (retrobulbar optic neuritis, central scotoma, optic atrophy on the side of the lesion and contralateral papilledema usually occurring in tumors of the frontal lobe of the brain which press downward) (Jarus and Feldon, 1982). Bakay (1984) emphasized that loss of smell perception is one of the first signs of olfactory meningiomas.

In general, tumors or other destructive lesions involving the olfactory bulb, tract, or prefrontal lobe may cause olfactory deficits. Temporal lobe tumors usually cause olfactory hallucinations. It is estimated that approximately 20% of the tumors of the temporal lobe produce some form of olfactory disturbance (Furstenberg et al., 1943). The presence of olfactory deficits correlates more with the location of tumors than the histology (Fig. 5).

I. Acquired Immunodeficiency Syndrome

Olfactory deficits of patients with human immunodeficiency virus (HIV) infection have been reported (Brody et al., 1991; Heald et al., 1998). These authors suggest that impaired olfaction might serve as a marker of early central nervous system HIV involvement. The principal histopathological abnormalities in the brain of acquired immunodeficiency syndrome (AIDS) patients are in the subcortical structures, predominantly in the central white matter, deep gray structures including the basal ganglia, the thalamus, and the brain stem (Petito et al., 1986; Price et al., 1988). Everall et al., (1991) have found that the neuronal numerical density in the frontal cortex is significantly lower in HIV patients than in controls—a loss of about 38% of neurons in the superior frontal gyrus in AIDS patients. This may account for the olfactory deficits in these patients.

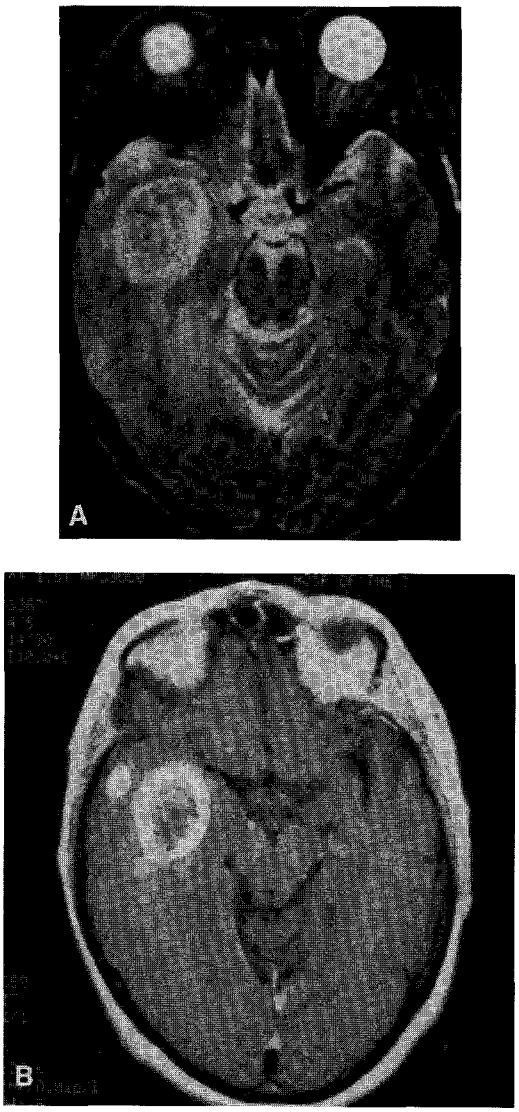

Figure 5 Temporal lobe mass in a 62-year-old woman with olfactory hallucinations. (A) T_2W MR scan reveals a relatively well-defined right temporal lobe mass with mild mass effect. (B) Contrast-enhanced T_1W MR image shows peripheral enhancement of the tumor with a satellite nodule laterally. Sulci are effaced and the temporal horn is obliterated.

Neuroradiological study has found that patients with HIV infection show widened cortical sulci, enlarged ventricles, cerebral atrophy, and brain stem atrophy when compared with controls (Brun et al., 1986; Elovaara et al., 1990; Post et al., 1988). Opportunistic infections and CNS lymphoma may be superimposal on these changes. The pathogenesis of the olfactory deficits of AIDS patients needs further investigating but most likely will relate to disease in the prefrontal lobe. In addition to CNS changes, sinusitis in HIV-infected patients is common and severe. Therefore, the possibility of peripheral cause of olfactory deficits in AIDS patients also has to be taken into account in certain cases.

J. Multiple Sclerosis

Multiple sclerosis (MS), a markedly debilitating neurological disease, affects millions of Americans in the prime of their lives. Though the influence of MS on the sense of smell has long been controversial, recent MRI studies (Doty et al., 1997, 1999) have demonstrated that the olfactory function in patients with MS is closely correlated with the number of demyelinating plaques within central olfactory processing areas of the brain, as determined by MRI (Fig. 6, 7). A strong negative relationship (Spearman $r = -0.94$) was found between scores on the University of Pennsylvania Smell Identification Test (UPSIT) and the number of plaques within the inferior frontal and temporal lobe regions (Doty et al., 1997). A close association was present, longitudinally, between the remission and exacerbation of plaque numbers and UPSIT scores, with lower UPSIT scores occurring during periods of exacerbation (Doty et al., 1999).

K. Other Central Causes

There are also reports of olfactory dysfunction in hypochondriasis, amyotrophic lateral sclerosis, epilepsy, and migraine (Doty et al., 1991b; Mott and Leopold, 1991). Although the pathogenesis of olfactory dysfunction in these disorders is still unclear, it appears that a central mechanism is involved, rather than a peripheral one.

VI. OVERVIEW AND DISCUSSION

It is apparent from the studies reviewed in this chapter and the information presented elsewhere in this volume that olfactory dysfunction can be due to numerous causes. Once an olfactory disorder has been recognized, the most important step in the diagnostic process is to determine the site of the lesion, i.e., anatomical localization. Unfortunately, current clinical olfactory testing is unable to localize the site of morphological changes (Doty et al., 1984). Modern medical imaging techniques can be of great value in the anatomical classification and localization of the common causes of olfactory dysfunction (Li et al., 1994). The most common source of olfactory dysfunction is the peripheral pathway (Goodspeed et al., 1987; Mott and Leopold. 1991). In the evaluation of peripheral causes, the "sinus series" radiographs offer limited information. At present, high-resolution CT, especially coronal scans, is

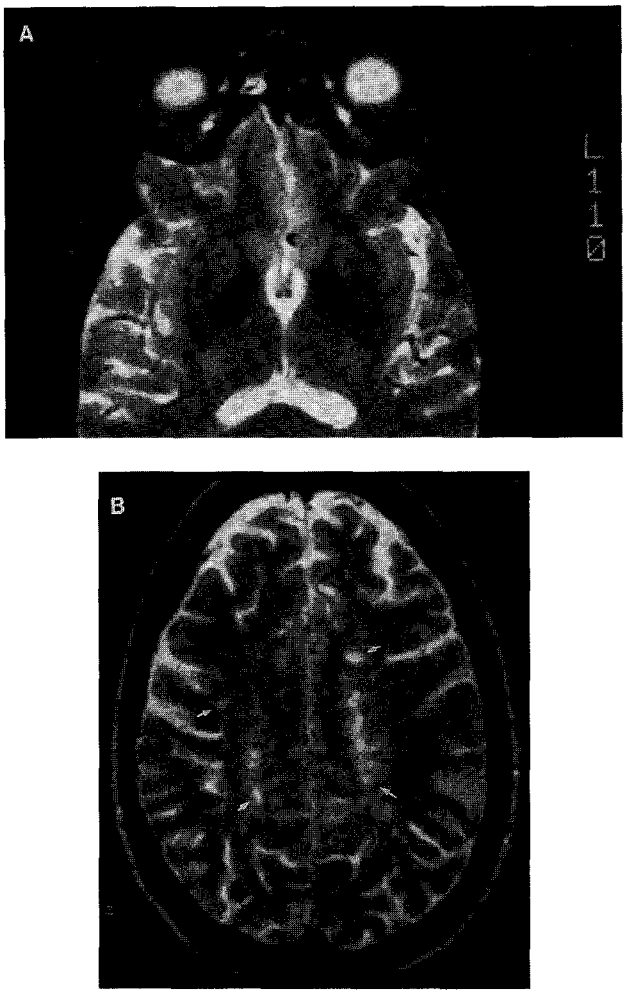

Figure 6 A 55-year-old MS patient with no significant olfactory dysfunction, as measured by the UPSIT. Axial T_2W MRI scan shows no obvious plaques in the inferior frontal and temporal lobe regions (A). Numerous plaques were identified in supraperiventricular regions (B).

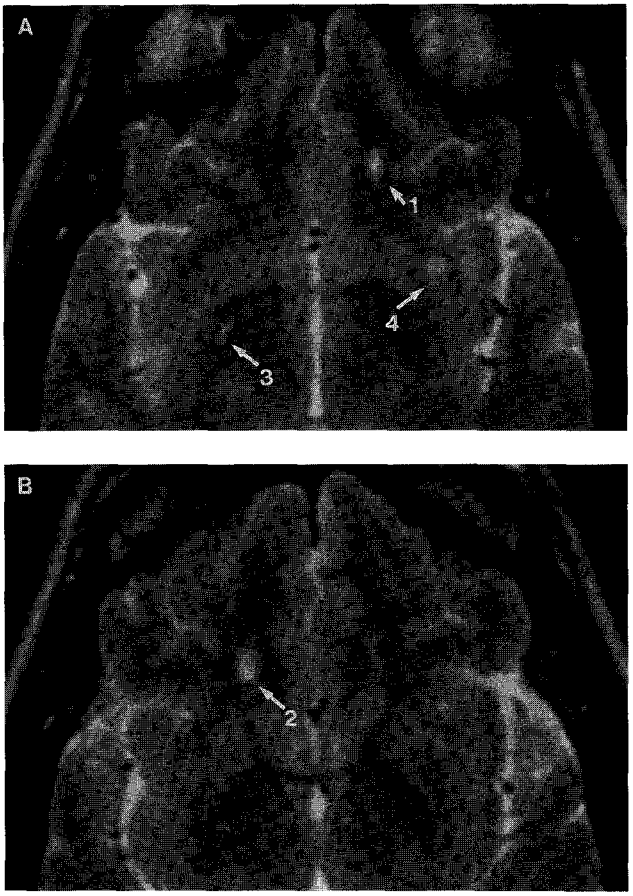

Figure 7 Axial T_2W MRI scans from a severely micrsomic (UPSIT = 20) 50-year-old man with an 8-year history of MS. The place of section in (A) is 6 mm below that of (B). Note the prominent plaques (10 × 5 mm each) within the posterior part of the white matter of the gyrus rectus of the L and R subfrontal lobe regions (arrows 1 and 2, respectively), and the relatively high signal intensity plaques in the subtemporal lobe regions (arrows 3 and 4).

the study of choice to look at the bony sinonasal structures and the ostiomeatal complex. CT can also provide important information as a road map, which may be needed for surgical treatment.

MRI possesses special ability in soft tissue discrimination and offers multiplanar capabilities. In the evaluation of the central causes of olfactory disturbances, MRI has a paramount role. Neuroimaging studies of patients with olfactory deficits related to neuropsychiatric problems have revealed interesting findings and possibly clues for understanding some of the links between olfactory deficits and pathophysiological changes of the brain. The neuroimaging findings of patients with AD, KP, or schizophrenia share some similarities. Thus, almost all of the abnormalities of the brain parenchyma revealed by neuroimaging studies in patients with AD, KP, or schizophrenia involve central brain areas that contain netrons of olfactory projections including areas of the prefrontal lobe, temporal lobe, hippocampus, and thalamus.

Recent studies have provided a clear physiological explanation for decreased olfactory function in patients with MS (Doty et al., 1997, 1998, 1999). Current studies from our laboratory suggest that MS, with its relatively discrete focal regions of demyelination lesion, may be of value in studying brain regions involved in sensory perception in addition to olfaction.

It is much more difficult to explain the olfactory dysfunction in PD patients, and presently imaging studies have been of little use in clarifying this matter. Loss of olfaction in these patients may be related to factors with dopamine

and dopamine receptors, although, as noted earlier, no return of function accompanies L-dopa treatment. In addition, pathological changes in the areas of putamen and caudate nuclei, which have fibers connected with limbic system and striatum, may contribute to the loss of the sense of smell. In this hypothesis, the olfactory dysfunction in PD patients might share a similar etiology to patients with HD.

In congenital disorders, such as Kallmann's syndrome, the cause of anosmia can be seen on MRI studies as the absence of olfactory bulbs (Yousem et al., 1993, 1996a). Other congenital abnormalities, such as choanal atresia and meningoencephaloceles, also can be detected by imaging studies (Klein et al., 1987; Moorman et al., 1984).

In the categories of head trauma and brain tumors, imaging studies have shown strong links between olfactory dysfunction and the location of the damaged brain. The histology of the tumor or traumatic injury is less critical than its location (Costanzo and Zasler, 1991; Jarrus and Feldon, 1982; Schellinger et al., 1983; Yousem et al., 1996b).

Hyposmia or anosmia induced by occupational or accidental exposure to toxins, as well as that induced by intranasal use of drugs such as cocaine, has been traditionally thought to be due to damage to the peripheral pathways. However, one study has suggested that olfactory deficits caused by occupational exposure to toxins may have both peripheral toxic and CNS effects (Schwartz et al., 1989). Imaging studies have shown CNS complications in cocaine abusers (Holman et al., 1991; Kalkow et al., 1988; Pascual-Leone et al., 1991; Tumeth et al., 1990), and one report of anosmia as a sequela of hydrogen sulfide (H_2S) inhalation suggested the loss to be due to central brain damage (Tvedt et al., 1991).

VII. SUMMARY

Medial imaging is an essential part of the evaluation of patients with olfactory disorders. In the assessment of the peripheral causes of olfactory deficits, medical imaging studies, especially CT and/or MRI, can reveal anatomical information and structural changes, suggest differential diagnosis, and provide the road map that may be needed for surgical intervention. On the other hand, in the evaluation of the central causes, MRI, fMRI, PET, or SPECT can provide information elucidating the links between olfactory dysfunction and the structural or functional changes in the living brain.

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REFERENCES

Alavi, A., and Hirsch, I. J. (1991). Studies of central nervous system disorders with single photon emission computed tomography and positron emission tomography: Evolution over the past 2 decades. *Semin. Nucl. Med.* 21:58–81.

Albert M, Naser M. A, Levine H. L, et al. (1984). Ventricular size in patients with presenile dementia of the Alzheimer's type. *Arch. Neurol.* 41:1258–1263.

Allphin AL, Strauss M, and Abdul-Karin F. W (1991). Allergic fungal sinusitis: Problems in diagnosis and treatment. *Laryngoscope* 101:815–820.

Atlas S. W, Braffman B. H, LoBrutto R, Elder D. E, Herlyn D (1990). Human malignant melanomas with varying degrees of melanin content in nude mice: MRI imaging, histopathology, and electron paramagnetic resonance. *I. Comput. Assist. Tomog.* 14:547–554.

Averback, P. (1983). Two new lesions in Alzheimer's disease. *Lancet* 2:1203.

Bakay L. (1984). Olfactory meningiomas: The missed diagnosis. *JAMA* 251:53–55.

Ball M. J, Fishman M, Hachinski V, et al. (1985). A new definition of Alzheimer's disease: A hippocampal dementia. *Lancet* 1: 14–16.

Barat J L (1990). Mucoceles of the sphenoidal sinus. Report of six cases and review of the literature. *J. Neuroradiol.* 17: 135–151.

Barkovich A J, Vandermark P, Edwards MSB, and Cogen P H (1991). Congenital nasal masses: C T and M R imaging features in 16 cases. *AJR* 156:587–598.

Barkovich A J, and Quint, D. J. (1993). Middle interhemispheric fusion: an unusual variant of holoprosencephaly. *AJNR* 14:431–440.

Baroody F. M, and Naclerio RM (1991). Allergic rhinitis. In *Smell and Taste in Health and Disease*, Getchell TV, et al. (Eds.). Raven Press, New York, pp. 529–552.

Benes F. M, Davidson J, and Bird E. D (1986). Quantitative cytoarchitectural studies of the cerebral cortex of schizophrenics. *Arch. Gen. Psychiatry* 43:31–35.

Bonte B. L, Tintner R, Weiner MF, et al. (1993). Brain blood flow in the dementias: SPECT with histopathologic correlation. *Radiology* 186:361–365.

Braffman B. H, Grossman R. I, Goldberg H. I, et al. (1989). MR imaging of Parkinson disease with spin-echo and gradient-echo sequences. *AJR* 152:159–165.

Brasch R. C (1992). New directions in the development of MR imaging contrast media. *Radiology* 183:1–11.

Brody D, Serby M, Etenne N, et al. (1991). Olfactory identification deficits in HIV infection. *Am. J. Psychiatry* 148:248–250.

Brooks D. J, Ibanez V, Playford E. D, et al. (1991). Presynaptic and postsynaptic striatal dopaminergic function in neuroacanthocytosis: A positron emission tomographic study. *Ann. Neurol.* 30:166–171.

Brun B, Boesen F, Gerstoft J, et al. (1986). Cerebral computed tomography in men with acquired immunodeficiency syndrome. *Acta Radiol.* 27:385–387.

Buchwald C, Nielsen L. H, Ahlgren P, et al. (1990). Radiologic aspects of inverted papilloma. *Eur. I. Radiol.* 10:134–139.

Carter B. L, and Runge V. S (1988). Imaging modalities for the study of paranasal sinuses and nasopharynx. *Otolaryngol. Clin. North Am.* 21:395–420.

Cohen W (1990). Recent developments in the imaging of neuraxis trauma. *Curr. Opin. Radiol.* 2:34–39.

Costanzo R. M, and Zasler N. D (1991). Head trauma. In *Smell and Taste in Health and Disease*, Getchell TV, et al. (Eds.). Raven Press, New York, pp. 711–730.

Cowart B. J, Flynn-Rodden K, McGeady S. J, and Lowery L. D (1993). Hyposomia in allergic rhinitis. *J. Allergy Clin. Immunol.* 91:747–751.

Crysdale WS (1981). Otorhinolaryngologic problems in patients with craniofacial anomalies. *Otolaryngol. Clin. North Am.* 14:145–155.

Daly B. D, Russell J. L, Davidson M. J, and Lamb J. T (1990). Thin section computed tomography in the evaluation of nasoethmoid trauma. *Clin. Radiol.* 41:1267–1272.

De Morsier G, and Gauthier G (1963). La dysplasie olfacto-genitale. *Path. Biol.* 11:(1)267–272.

de Leon M. J, McRae T, Tsai JR, et al. (1988). Abnormal cortical response in Alzheimer's disease linked to hippocampal atrophy. *Lancet* 2:391–392.

de Leon M. J, George A. E, Reisberg B, et al. (1989). Alzheimer's disease: Longitudinal CT studies of ventricular change. *AJR* 153:1257–1262.

Deems D. A, Doty R. L, Settle R. G, et al. (1991). Smell and taste disorders: A study of 750 patients from the University of Pennsylvania Smell and Taste Center. *Arch. Otolaryngol. Head Neck Surg.* 117:519–528.

Di Rienzo, L., Artuso, A., and Colosino, C. (2002). Isolated congenital agenesis of olfactory bulbs and tracts in a child without Kallman's syndrome. *Ann. Otol. Rhinol-Larygol.* 111:657–660.

Donnal J. F, Heinz E. R, and Burger P. C (1990). MR of reversible thalamic lesions in Wernick's syndrome. *AJNR* 11: 893–894.

Doty RL (1991). Olfactory dysfunction in neurodegenerative disorders. In *Smell and Taste in Health and Disease*, Getchell TV, et al. (Eds.). Raven Press, New York, pp. 735–751.

Doty R. L, Frye R (1989). Influence of nasal obstruction on smell function. *Otolaryngol. Clin. North Am.* 22:397–411.

Doty, R.L. & Mishra, A. (2001). Influences of nasal obstruction, rhinitis, and rhinosinusitis on the ability to smell. *Laryngoscoppe* 111:409–423.

Doty R. *and Practice of Rhinology*, Goldman J (Ed.). John Wiley & Sons, New York, pp. 761–785.

Doty RL, Shaman P, and Dann M (1984). Development of the University of Pennsylvania Smell Identification Test: A standardized microencapsulated test of olfactory function. *Physiol. Behav. (Monogr.)* 32:489–502.

Doty R. L, Reyes P. F, and Gregor T (1987). Presence of both odor identification and detection deficits in Alzheimer's disease. *Brain Res. Bull.* 18:597–600.

Doty R. L, Deems D. A, Stellar S (1988). Olfactory dysfunction in parkinsonism: A general deficit unrelated to neurologic signs, disease stage, or disease duration. *Neurology* 38: 1237–1244.

Doty R. L, Bartoshuk L. M, and Snow J. B Jr (1991). Causes of olfactory and gustatory disorders. In *Smell and Taste in Health and Disease*, Getchell TV, et al. (eds.). Raven Press, New York, pp. 449–462.

Doty R. L, Kimmelman C. P, and Lesser R. P (1992a). Smell and taste and their disorders. In *Diseases of the Nervous System: Clinical Neurobiology*, Vol. 1, Asbury AK, Mckhann GM, and McDonald WI (Eds.), W.B. Saunders, Philadelphia, pp. 390–403.

Doty, R. L, Stern M. B, Pfeiffer C, et al. (1992b). Bilateral olfactory dysfunction in early stage medicated and unmedicated idiopathic Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry* 55:138–142.

Doty, R. L, Bromley, S. M, Stern, MB (1995). Olfactory testing as an aid in the diagnosis of Parkinson's disease: development of optimal discrimination criteria. *Neurodegeneration* 4:93–97.

Doty R. L, Li C, Mannon L. J, and Yousem D. M (1997a). Olfactory dysfunction in multiple sclerosis [published erratum appears in N Engl J Med 1997; 337(7):507]. *N. Engl. J. Med.* 336:1918–1919.

Doty R. L, Yousem D. M, Pham L. T, et al. (1997b). Olfactory dysfunction in patients with head trauma. *Arch. Neurol.* 54:1131–1140.

Doty R. L, Li C, Mannon L. J, and Yousem D. M (1999). Olfactory dysfunction in multiple sclerosis: Relation to longitudinal changes in plaque numbers in central olfactory structures. *Neurology* 53:880–882.

Drayer B. P, Olanow W, Burger P, et al. (1986). Parkinson plus syndrome diagnosis using high field MR imaging of brain iron. *Radiology* 159:493–498.

Drutman J, Babbel RW, Harnsberger HR, et al. (1991). Sinonasl polyposis. *Semin. Ultrasound CT MR* 12:561–574.

Elkon D, Hightower S. I, Lim ML, et al. (1979). Esthesioneuroblastoma. *Cancer* 44:1087–1094.

Elovaara I, Poutiainen E, Raininko R, et al. (1990). Mild brain atrophy in early HIV infection: The lack of association with cognitive deficits and HIV-specific intrathecal immune response. *I. Neurol. Sci.* 99:121–136.

Esiri M. M, and Wilcock G. M (1984). The olfactory bulbs in Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry* 47:56–60.

Everall I. P, Lutherat P. J, and Lantos P. L (1991). Neuronal loss in the frontal cortex in HIV infection. *Lancet* 337:1119–1121.

Falkai P, Bogerts B, and Rozumek M (1988). Limbic pathology in schizophrenia: The entorhinal region — a morphometric study. *Biol. Psychiatry* 24:515–521.

Fowler J. S, Hoffman E. J, Larson S. M, et al. (1988). Positron emission tomography: A new approach to brain chemistry. *JAMA* 206:2704–2710.

Furstenberg A. C, Crosby E, and Farrior B (1943). Neurologic lesions which influence the sense of smell. *Arch. Otolaryngol.* 38:529–530.

Gallucci M, Bozzao A, Splendiani A, et al. (1990). Wernicke encephalopathy: MR findings in five patients. *AJR* 155:1309–1314.

George A. E, deLeon M. J, Ferris S. H, et al. (1981). Parenchymal CT correlates of senile dementia (Alzheimer's disease): Loss of grey-white discriminality. *AJNR* 2:205–213.

George A. E, de Leon MJ, Rosenbloom S, et al. (1983). Ventricular volume and cognitive deficit: A computed tomographic study. *Radiology* 149:493–498.

George A. E, de Leon M. J, Stylopoulos L. A, et al. (1990). CT diagnostic features of Alzheimer disease: Importance of the choroidal/hippocampal fissure complex. *AJNR* 11:101–107.

Goodspeed, R. B, Gent, J. F, Leonard G, et al. (1987). The prevalence of abnormal paranasal sinus x-rays in patients with olfactory disorders. *Conn. Med.* 51:1–3.

Gordon, A. S, Moran, D. T, Jajek, VW, et al (1990). The effect of chronic cocaine abuse on human olfaction. *Arch. Otolaryngol. Head Neck Surg.* 116:1415–1418.

Graamans, K, and Slootweg, P. J. (1989). Orbital exenteration in surgery of malignant neoplasms of the paranasal sinuses. The value of preoperative computed tomography. *Arch. Otolaryngol. Head Neck Surg.* 115:977–980.

Gregler, L. L, and Mark, H (1986). Medical complications of cocaine abuse. *N. Engl. J. Med.* 315:1495–1500.

Gussack, G. S, and Hudgins, P. A. (1991). Imaging modalities in recurrent head and neck tumors. *Laryngoscope* 101:119–124.

Hagan, P. J (1967). Post-traumatiac anosmia. *Arch. Otolaryngol.* 85:107–111.

Happer, C, Kril, J, Daly J (1987). Are we drinking our neurones away? *Br. Med. J.* 294:534–536.

Harris, G. J, Schlaepfer, T. E, Peng, L. W, Lee S, Federman, E. B, and Pearlson G. D (1994). Magnetic resonance imaging evaluation of the effects of ageing on grey-white ratio in the human brain. *Neuropathol. Appl. Neurobiol.* 20: 290–293.

Harris, GJ, Aylward, E. H, Peyser C. E, et al. (1996). Single photon emission computed tomographic blood flow and magnetic resonance volume imaging of basal ganglia in Huntington's disease. *Arch. Neurol.* 53:316–324.

Harris, G. J, Lewis, R. F, Satlin, A, et al. (1998). Dynamic susceptibility contrast MR imaging of regional cerebral blood volume in Alzheimer disease: a promising alternative to nuclear medicine. *AJNR* 19:1727–1732.

Harrison, P. J (1986). The pathogenesis of Alzheimer's disease: Beyond the cholinergic hypothesis. *J. Roy. Soc. Med.* 79:347–351.

Hayden, M. R, Martin, W. R. W, Stoessl, A. J, et al. (1986). Positron emission tomography in the early diagnosis of Huntington's disease. *Neurology* 36:888–894.

Heald A. E, Piper C. F, and Schiffman SS (1998). Taste and smell complaints in HIV-infected patients. *AIDS* 12:1667–1674.

Healy B (1992). From form to function — better imaging techniques extend study of living system (from NIH). *JAMA* 267: 2863.

Holman B. L, Carvalho P. A, Mendelson J, et al. (1991). Brain perfusion is abnormal in cocaine-dependent polydrug users: A study using Technetium-99m-HMPAO and ASPEC. *J. Nucl. Med.* 32:1206–1210.

Hunink, M. G, de Slegte, R. G, Gerritsen, G. J, Speelman, H (1990). CT and MRI assessment of tumors of the nose and paranasal sinuses, the nasopharynx and the parapharyngeal space using R0C methodology. *Neuroradiology* 32:220–225.

Hyman, B. T, Van Hoesen, G. W, and Damasio, A. R (1984). Alzheimer's disease: Cell-specific pathology isolates the hippocampel formation. *Science* 225:1168–1170.

Jacobson, R. R, and Lishman, W. A (1990). Cortical and diencephalic lesions in Korsakoff's syndrome: A clinical and CT scan study. *Psychol. Med.* 20:63–75.

Jafek, B. W, Eller, P. M, Johnson, E. W, et al. (1992). Ultrastructural changes of the olfactory epithelium in Alzheimer's disease. *Am. J. Rhinol.* 6:219–225.

Jagust, W. J, and Eberling, J. L (1991). MRI, CT, SPECT, PET: Their use in diagnosing dementia. *Geriatrics* 46:28–35.

Jarus, G. D, and Feldon, S. E (1982). Clinical and computer tomographic findings in the Foster Kennedy syndrome. *Am. J. Ophthalmol.* 93:317–322.

Jernigan, T. L, Schafer, K, Butters, N, and Cermak, LS (1991). Magnetic resonance imaging of alcoholic Korsakoff patients. *Neuropsychopharmacology* 4:175–186.

Jolles, P. R, Chapman, P. R, and Alavi, A (1989). PET, CT, and MRI in the evaluation of neuropsychiatric disorders: Current applications. *J. Nucl. Med.* 30:1589–16.

Jones, B. P, Moskowitz, H. R, Butters N, et al. (1975). Psychophysical scaling of olfactory visual and auditory stimuli by alcoholic Kosakoff's patients. *Neuropsychologica* 13: 387–393.

Joyce, E. M, and Robbins, T. W (1991). Frontal lobe function in Korsakoff and non-Korsakoff alcoholics' planning and spatial working memory. *Neuropsychologica* 29:709–723.

Kallmann, F. J, Schoenfeld, W. A, and Barrera, S. E (1944). The genetic aspects of primary eunuchoidism. *Am. J. Ment. Defic.* 48:203–221.

Kassel, E. E (1988). Traumatic injuries of the paranasal sinuses. *Otolaryngol. Clin. North Am.* 21:455–493.

Kelly, A. B, Zimmerman, R. D, Snow, R. B, et al. (1988). Head trauma: Comparison of MR and CT—experience in 100 patients. *AJNR* 9:699–708.

Kern, R. C. (2000). Chronic sinusitis and anosmia: pathologic changes in the olfactory mucosa. *Laryngoscope* 110: 1071–1077.

Kesslak, J. P, Nalcioglu, O, and Cotman, C. W (1991). Qualification of magnetic resonance scans for hippocampal and parahippocampal atrophy in Alzheimer's disease. *Neurology* 41: 51–54.

Kido, D. K, Caine, E. D, LeMay M, et al. (1989). Temporal lobe atrophy in patients with Alzheimer's disease: A CT study. *AJNR* 10:551–555.

Kimmelman, C. P (1991). Medical imaging of smell and taste disorders. In *Smell and Taste in Health and Disease*, Getchell TV, et al. (Eds.). Raven Press, New York, pp. 471–479.

Klein, V. R, Friedman, J. M, Brookshire, G. S, et al. (1987). Kallmann's syndrome associated with choanal atresia. *Clin. Genet.* 31:224–227.

Klingmuller, D, Dewes W, Krabe T, et al. (1987). Magnetic resonance imaging of the brain in patients with anosmia and hypothalamic hypogonadism (Kallmann's syndrome). *J. Clin. Endocrinol. Metab.* 65:581–584.

Kolkow, N. D, Mullani, N, Gould, K. L, et al. (1988). Cerebral blood flow in chronic cocaine users: A study with positron emission tomog. *Br. J. Psychiatry* 152:641–648.

Kopelman, M. D (1991). Frontal dysfunction and memory deficits in the alcoholic Korsakoff syndrome and Alzheimer-type dementia. *Brain* 114:117–137.

Kraus, D. H, Lanzieri, C. F, Wanamaker, J. R, Little, J. R, and Lavertu P (1992). Complementary use of computed tomography and magnetic resonance imaging in assessing skull base lesions. *Laryngoscope* 102:623–629.

Kuriloff, D. B (1989). Nasal septal perforation and nasal obstruction. *Otolaryngol. Clin. North Am.* 22:333–350.

Lanzieri, C. F., Shah, M., Krauss, D., and Lavertu, P. (1991). Use of gadolinium-enhanced MR imaging for differentiating mucoceles from neoplasms in the paranasal sinuses. *Radiology* 178:425–428.

Leigh, A. D (1943). Defects of smell after head injury. *Lancet* 1:38–40.

Levin, H. S, High, W. M, and Eisenberg, H. M (1985). Impairment of olfacory recognition after closed head injury. *Brain* 108:579–591.

Li C, Yousem, D. M, Hayden RE, and Doty RL (1993). Olfactory neuroblastomas: MR evaluation. *AJNR* 14:1167–1171.

Li C, Yousem DM, Doty RL, and Kennedy DW (1994). Neuroimaging in patients with olfactory dysfunction. *AJR* 162:411–418.

Lieblich, J. M, Rogol, A. D, White, B. J, et al. (1982). Syndrome of anosmia with hypogonadism Kallmann's syndrome) *Am. J. Med.* 73:506–519.

Loury, M. C, and Kennedy, D. W (1991). Chronic sinusitis and nasal polyposis. In *Smell and Taste in Health and Disease*, Getchell TV, et al. (Eds.). Raven Press, New York, pp. 517–528.

Lloyd, G. A, and Barker, P. B. (1991). Subtraction magnetic resonance for tumors of the skull base and sinuses: a new imaging technique. *J. Laryngol. Otol.* 105:628–631.

Lloyd, G. A. S, Lund, V. J, Phelps, P. D, Howard, D. J. (1987). MRI in the evaluation of nose and paranasal sinus diseases. *Br. J. Radiol.* 60:957–968.

Lyons, B. M, Donald, P. J. (1991). Radical surgery for nasal cavity and paranasal sinus tumors. *Otolaryngol. Clin. North Am.* 24:1499–1521.

Mair, R. G, Doty, R. L, Kelly, K. M, et al. (1986). Multimodel sensory discrimination deficits in Korsakoff's psychosis. *Neuropsychologica* 24:831–839.

Mair, G. R, Knoth, R. L, Rabchenuk, S. A, et al. (1991). Impairment of olfactory auditory, and spatial serial reversal learning in rats recovered from pyrithiamine-induced thiamine deficiency. Behav. Neurosci. 105:360–374.

Males, J. L, Townsend, J. L, and Schneider, R. A (1973). Hypogonadotrophic hypogonadism with anosmia — Kallmann's syndrome. *Arch. Int. Med.* 131:501–507.

Masters, S. J, McClean, P. M, Arcarese, J. S, et al. (1987). Skull x-ray examinations after head trauma. Recommendations by multidisciplinary panel and validation study. *N. Engl. J. Med.* 316:84–91.

Mathog, R. H (1992). *Atlas of Craniofacial Trauma*. W.B. Saunders Co., Philadelphia, pp. 377–379.

McAlister, W. H, Lusk R, Muntz, H. R (1989). Comparison of plain radiographs and coronal CT scans in infants and children with recurrent sinusitis. *AJR* 153:1259–1264.

McDonald, W. M, Krishnan, K. R, Doraiswamy, P. M, et al (1991). Magnetic resonance findings in patients with early-onset Alzheimer's disease. *Biol. Psychiatry* 29:799–810.

Mehra, Y. N; Mann, S. B; Dubey, S. P; Suri S. (1989). Computed tomography for determining pathways of extension and a staging and treatment system for juvenile angiofibromas. *Ear Nose Throat J.* 68:576–589.

Mesulam, M. M (1990). Schizophrenia and the brain. *N. Engl. J. Med.* 322:842–845.

Metter, E. J, Kempler D, Jackson C, et al. (1989). Cerebral glucose metabolism in Wernickes's, Broca's, and conduction aphasia. *Arch. Neurol.* 46:27–34.

Moberg, P. J, Pearlson, G. D, Speedie, L. J, et al. (1987). Olfactory recognition: Differential impairments in early and late Huntington's and Alzheimer's dtsease. *J. Clin. Exp. Neuropsychol.* 9:650–664.

Montgomery, E. B, Koller, W. C, LaMantia, T. J, et al. (2000). Early detection of probable idiopathic Parkinson's disease: Development of a diagnostic test battery. *Movement Disord.* 15:467–473.

Moorman, J. R, Crain B, and Osborne D (1984). Kallmann's syndrome with associated cardiovascular and intracranial anomalies. *Am. J. Med.* 77:369–372.

Mott, A. E, and Leopold, D. A (1991). Disorders in taste and smell. *Med. Clin. North Am.* 75:1321–1353.

Myers, R. H, Vonsattell, J. P, Paskevich, P. A, et al (1991). Decreased neuronal and increased oligodendroglial densities in Huntington's disease caudate nucleus. *J. Neuropathol. Exp. Neurol.* 50:729–742.

Nagel, J. S, Johnson, K. A, Ichise M, et al. (1988) Decreased iodine-123 IMP caudate nucleus uptake in patients with Huntington's disease. *Clin. Nucl. Med.* 13:486–496.

Naser, M. A, Gebhardt C, and Levine, H. L (1980). Decrease computerized tomography numbers in patients with presenile dementia. *Arch. Neurol.* 37:401–409.

Newbill, E. T, Johns, M. E, Cantrel,l R. W (1985). Esthesioneuroblastoma: Diagnosis and management. *South. Med. J.* 78:275–282.

Newman, N. M, DiLoreto, D. A, Ho, T. I, et al. (1988). Bilateral optic neuropathy and osteolytic sinusitis. Complications of cocaine abuse. *JAMA* 259:72–74.

Ohm, T. G, Braak H (1987). Olfactory bulb changes in Alzheimer's disease. *Acta Neuropathol. (Berlin)* 73:365–369.

Ohnishi, T, Hoshi, H, Nagamachi S, et al. (1991) Regional cerebral blood flow study with ^{123}I-IMP in patients with degenerative dementia. *AJNR* 12:513–520.

Paling, M. R, Black, W. C, Levine, P. A, et al. (1987). Tumor invasion of the anterior skull base: A comparison of MR and CT studies. *J. Comput. Assist. Tomogr.* 11:824–830.

Parker, G. D, and Harnsberger, H. R (1991). Clinical-radiologic issues in perineural tumor spread of malignant diseases of the extracranial head and neck. *RadioGraphics* 11:383–399.

Pascual-Leone A, Dhuna A, and Anderson D (1991). Cerebral atrophy in habitua cocaine abusers: A planimetric CT study. *Neurology* 41:34–38.

Pearson, R. C. A, and Powell, T. P. S (1989). The neuroanatomy of Alzheimer's disease. *Rev. Neurosci.* 2:101–122.

Petito, C. K, Cho E-s, Lemann W, et al. (1986). Neuropathology of acquired immunodeficiency syndrome (AIDS): An autopsy review. *J. Neuropathol. Exp. Neurol.* 45:635–646.

Pfefferbaum, A., Sullivan, E. V., Mathalon, D. H., Shear, P. K., Rosenbloom, M. J., and Lim, K. O. (1995). Longitudinal changes in magnetic resonance imaging brain volumes in abstinent and relapsed alcoholics. *Alcoholism: Clinical and Experimental Research* 19:1177–1191.

Phillips, P. P, Gustafson, R. O, and Facer, G. W (1990). The clinical behavior of inverting papilloma of the nose and paranasal sinuses: Report of 112 cases and review of the literature. *Laryngoscope* 100:463–469.

Post, M. J. D, Tate, L. G, Quencer, R. M, et al. (1988). CT, MR, and pathology in HIV encephalitis and meningitis. *AJR* 151: 373–380.

Potter, H, and Butters, N (1980). An assessment of olfactory deficits in patients with damage to prefrontal cortex. *Neuropsychologica* 18:621–628.

Price, J. L (1985). Beyond the primary olfactory cortex: Olfactory-related areas in the neocortex, thalamus and hypothalamus. *Chem. Senses* 10:239–258.

Price, J. L (1990). Olfactory system. In *The Human Nervous System*, Paxinos, G. (Ed.). Academic Press, Inc., San Diego pp. 979–998.

Price, R. W, Brew B, Sidtis J, et al (1988). The brain in AIDS: Central nervous system HIV-I infetion and AIDS dementia complex. *Science* 239:586–592.

Rausch R, and Serafetinides, E. A (1975). Specific alteration of olfaction in humans with temporal lobe lesions. *Nature* 255:557–558.

Rausch R, Serafetinides, E. A, Crandall PH (1977). Olfactory memory in patients with anterior temporal lobectomy. *Cortex* 13:445–452.

Reid, I. C, Besson, J. A. O, Best, P. V, et al. (1988). Imaging of cerebral blood flow markers in Huntington's disese using single photon emission computed tomography. *J. Neurol. Neurosurg. Psychiatry* 51:1264–1268.

Reiman, E. M, and Mintun, M. A (1990). Positron emission tomography (editorials). *Arch. Intern. Med.* 150:729–731.

Roberts, G. W (1988). Abnormalities in brain structure in schizophrenia. *Curr. Opin. Psychiatry* 1:83–89.

Ron, M. A (1983). The alcoholic brain: CT scan and psychological findings. *Psychol. Med. Monograph*, Supplement 3.

Ron, M. A, Acker W, Shaw GK, et al. (1982). Computerized tomography of the brain in chronic alcoholics: A survey and follow-up study. *Brain* 105:497–514.

Schechter PJ, and Henkin RI (1974). Abnormalities of taste and smell after head trauma. *J. Neurol. Neurosurg. Psychiatry* 37: 802–810.

Schellinger D, Henkin RT, and Smirniotopoulos JG (1983). CT of the brain in taste and smell dysfunction. *AJNR* 4:7 52–754.

Schwartz, B, Doty, R. L, Frye, R. E, et al. (1989). Olfactory function in chemical workers exposed to acrylate and methacrylate vapors. *Am. J. Public Health* 79:613–618.

Schweitzer, V. G (1986). Osteolytic sinusitis and pneumomediastinum: Deceptive otolaryngologic complications of cocaine abuse. *Laryngoscope* 96:206–210.

Serby M, Larson P, and Kalkstein, D (1990). Olfactory sense in psychoses. *Biol. Psychiatry* 28:830.

Serby, M, Larson, P, and Kalkstein, D (1991). The nature and course of olfactory deficits in Alzheimer's disese. *Am. J. Psychiatry* 148:357–360.

Shapiro, M. D, and Som, P. M (1989). MRI of the paranasal sinuses and nasal cavity. *Radiol. Clin. North Am.* 27: 447–475.

Simmons, J. T, Pastakia B, Chase, T. N, et al. (1986). Magnetic resonance imaging in Huntington's disease. *Am. J. Neuroradiol.* 7:25–28.

Sisson, G. A Sr, Toriumi, D. M, and Atiyah, R. A. (1989). Paranasal sinus malignancy; a comprehensive update. *Laryngoscope* 99:143–150.

Som, P. M (1991). Tumors and tumor-like conditions. In *Head and Neck Imaging*, 2nd ed., Som PM (Ed.). Mosby-Year Book Inc., St. Louis, pp. 169–227.

Som, P. M, Shapiro, M. D, Biller, H. F, et al. (1988). Sinonasal tumors and inflammatory tissues: Differentiation with MR imaging. *Radiology* 167:803–808.

Som, P. M, Dillon, W. P, Curtin, H. D, et al. (1990). Hypointense paranasal sinus foci: Differential diagnosis with MR imaging and relation to CT findings. *Radiology* 176:777–781.

Squire, L. R, Amaral, D. G, and Press, G. A (1990). Magnetic resonance imaging of the hippocampal formation and mammillary nuclei distinguish medial temporal lobe and diencephalic amnesia. *J. Neurosci.* 10:3109–3117.

Starkstein, S. E, Folstein, S. E, Brandt J, et al. (1989) Atrophy in Huntington's disease: A CT-scan study. *Neuroradiology* 31:156–159.

Suddath, R. L, Casanova, M. F, Goldberg, T. E, et al. (1989). Temporal lobe pathology in schizophrenia. A quantitative magnetic resonance imaging study. *Am. J. Psychiatry* 146:464–472.

Sumner, D (1964). Post-traumatic anosmia. *Brain* 87:107–120.

Suzuki, M, Takashima T, Kadoya M, et al. (1989). MR imaging of olfactory bulbs and tracts. *AJNR* 10:955–957.

Tanabe, T, Jino M, Takagi SF (1975). Discremination of odors in olfactory bulb, pyriform-amygdaloid areas, and orbitofrontal cortex of the monkey. *J. Neurophysiol.* 38:1284–1296.

Tumeth, S. S, Nagel, J. S, English RJ, et al. (1990). Cerebral abnormalities in cocaine abusers: demonstration by SPECT perfusion brain scintigraphy. *Radiology* 176:821–824.

Turetsky, B. I, Moberg, P. J, Yousem, D. M, et al. (2000). Reduced olfactory bulb volume in patients with schizophrenia. *Am. J. Psychiatry* 157:828–830.

Tvedt, B. Skyberg, K, Aaserud, O, et al. (1991). Brain damage caused by hydrogen sulfide: A follow-up study of six patients. *Am. J. Int. Med.* 20:91–101.

Van Tassel, P, Lee, Y. Y. (1991). Gd-DTPA enhanced MRI for detecting intracranial extension of sinonasal malignancies. *J. Comput. Assist. Tomogr.* 15:387–392.

Victor, M (1990). MR in the diagnosis of Wernicke-Korsakoff syndrome. *AJR* 1315–1316.

Vogl, T, Dresel S, Bilaniuk LT, et al. (1990) Tumors of the nasopharynx and adjacent areas: MR imaging with Gd-DTPA. *AJNR* 11:187–194.

Vonsattel, J. P, Myers, R. H, Stevens, T. J, et al. (1985). Neuropathological classification of Huntington's disease. *J. Neuropathol. Exp. Neurol.* 44:559–577.

Young AH, Blackwood DHR, Roxborough H, et al. (1991). A magnetic resonance imaging study of schizophrenia: Brain structure and clinical symptoms. *Br. J. Psychiatry* 158–164.

Yousem, D. M, Fellows, D. W, Kennedy, D. W, et al. (1992). Inverted papilloma: MR evaluation. *Radiology* 185:501–505.

Yousem, D. M, Li, C, Turner, W. J. D, et al. (1993). Kallmann's syndrome: MR evaluation of olfactory system. *AJNR* 14:839–843.

Yousem, D. M, Geckle, R. J, Bilker W, McKeown DA, Doty RL. (1996a). MR evaluation of patients with congenital hyposmia or anosmia. *AJR* 166:439–443

Yousem, D. M, Geckle R. J, Bilker WB, McKeown DA, and Doty RL. (1996b). Posttraumatic olfactory dysfunction: MR and clinical evaluation. *AJNR* 17:1171–1179

Yousem, D. M., Li, C., Montone, K.T., et al. (1996c). Primary malignant melanoma of the sinonasal cavity: MR imaging evaluation. *RadioGraphics* 16:1101–1110.

Yousem, D. M., Geckle, R. J., Doty, R. L. & Bilker, W. B. (1997a). Reproducibility and reliability of volumetric measures of olfactory eloquent structures. *Acad. Radiol.* 4:264–269.

Yousem, D. M., Williams, S. C. R., Howard, R. O., Andrew, C., Simmons, A., Allin, M., Geckle, R.J., Suskin, D., Bullmore, E. T., Brammer, M. J. & Doty, R. L. (1997b). Functional MRI imaging during odor stimulation: Preliminary data. *Neuroradiology* 204:833–838.

Yousem, D. M., Geckle, R. J., Bilker, W. B. & Doty, R. L. (1998). Olfactory bulb and tract and temporal lobe volumes: Normative data across decades. *Ann. NY Acad. Sci.* 855:546–555.

Yousem, D. M., Geckle, R. J., Bilker, W. B., Kroger, H. & Doty, R.L. (1999a). Posttraumatic smell loss: Relationship to psychophysical tests and volumes of the olfactory bulbs and tracts and the temporal lobes. *Acad. Radiol.* 6:264–272.

Yousem, D. M., Maldjian, J. A., Hummel, T., Alsop, D. C., Geckle, R. J., Kraut, M. A., Doty, R. L. (1999b). The effect of age on odor-stimulated functional magnetic resonance imaging. *Am. J. Neuroradiol.* 20:600–608.

Yousem, D. M., Maldjian, J. A., Siddiqi, F., Hummel, T., Alsop, D. C., Geckle, R. J., Bilker, W. B., and Doty, R. L. (1999c). Gender effects on odor-stimulated functional magnetic resonance imaging. *Brain Res.* 818:480–487.

Zimmerman, R A, Bilaniuk, L. T, Hackney, D. B, et al. (1986). Head injury: early results of comparing CT and high-field MR. *AJR* 147:1215–1222.

Zinreich, S. J., Kennedy, D. W., Roenbaum, A. E., et al. (1987). Paranasal sinuses: CT imaging requirements for endoscopic surgery. *Radiology* 163:769–775.

Zusho, H. (1982). Post-traumatic anosmia. *Arch. Otolaryngol.* 108:90–92.