REVIEW

Studies of Human Olfaction from the University of Pennsylvania Smell and Taste Center

Richard L. Doty

Smell and Taste Center, University of Pennsylvania Medical Center, Philadelphia, PA 19104, USA

Correspondence to be sent to: R.L. Doty, Smell and Taste Center, University of Pennsylvania Medical Center, 3400 Spruce Street, Philadelphia, PA 19104, USA

Abstract

This paper, presented in part as an invited lecture on the occasion of Professor E.P. Koster's retirement from Utrecht University, summarizes a large body of human studies performed at the University of Pennsylvania Smell and Taste Center during the last 17 years. Details of the development of standardized olfactory tests are provided, including their validation and application in a wide variety of clinical and laboratory settings. Included are studies related to transduction mechanisms in olfactory coding and factors that adversely influence olfactory function (e.g. age, gender, smoking, exposure to environmental chemicals, numerous diseases). A brief discussion of the strengths and weaknesses of the olfactory vector hypothesis for neurodegenerative diseases is also presented. Chem. Senses 22: 565-586, 1997.

Introduction

I am greatly honored to have the opportunity to participate in this celebration of Professor E.P. Köster (hereafter EP) and his contributions to the field of olfactory science. Since the early studies of Hans Zwaardemaker, Utrecht has been a major international center of olfactory research and has set the tone for understanding both basic and applied aspects of chemosensation. EP, along with his numerous colleagues, including Harry Koelga and Jan Kroeze, has been the modern standard bearer of this historical tradition and, despite considerable administrative pressures, has kept Utrecht on the forefront of human psychophysical research for many years. Thankfully his legacy will continue not only through his students and colleagues, but through his step children, the Chemical Senses journal, the European Chemoreception Research Organization (ECRO) and the European Center for Chemosensory Research in Dijon.

This afternoon I provide an overview of studies performed at the University of Pennsylvania Smell and Taste Center in the fields of human psychophysics and clinical olfaction, a number of which were influenced by EP's contributions to the psychophysical literature in the mid-1970s (e.g. Köster, 1975). As you may be aware, the University of Pennsylvania Smell and Taste Center, founded 17 years ago by a team consisting of EP's close personal
friend and colleague, the late David Moulton, as well as James B. Snow, Jr, R. Gregg Settle and myself, was the first of five such centers in the United States funded by the National Institutes of Health to better understand the senses of taste and smell in health and disease. (The other NIDCD-funded Centers are located at Jefferson Medical Center, Philadelphia (in conjunction with the Monell Chemical Senses Center), the State University of New York, Syracuse, the University of Colorado, Denver, and the University of Connecticut, Farmington.)

Despite the success of these specialized centers and our increased understanding of the olfactory system and its dysfunction, the impact of olfactory pathology is still not generally appreciated by the medical and lay communities. Altered smell function is not inconsequential, as olfaction plays a significant role in aesthetics, in the determination of flavor and in protection from spoiled foods, leaking natural gas, polluted air and smoke. Thus, it is perhaps not surprising that 68% of 750 consecutive patients who presented to the Center with primarily olfactory problems reported their dysfunction significantly altered their quality of life, 46% indicated that the disorder changed either their appetite or body weight and 56% complained that it influenced their daily living and/or psychological well-being (Deems et al., 1991).

Quantitative clinical olfactory testing

Although quantitative tests, such as Zwaademaker’s draw-tube olfactometer developed at Utrecht in the late 1800s (Zwaardemaker, 1889), have been used by a small number of comparatively enlightened physicians over the last century, such assessments have been the exception rather than the rule. Traditionally, if testing is done at all, the clinician asks a patient to sniff a few small vials containing odorants such as coffee, peppermint or raw tobacco, and to report whether an odor is perceived. Unfortunately, this procedure is akin to testing vision by shining a bright light into the patient’s eye and asking whether it can be seen. This problem is not rectified by requiring the patient to identify the stimuli, since, without cuing or multiple choices, even normal subjects have difficulty identifying many common odorants.

At the time of the Center’s founding in 1980, it was apparent to us, just as it had been to Hans Zwaademaker nearly a century earlier, that an accurate, practical and valid means of assessing olfactory function in the clinic was sorely needed. As in the case of audition, vision, and the other senses, quantitative olfactory assessment is essential to (i) establish the validity of a patient’s complaint; (ii) characterize the specific nature of the problem; (iii) reliably assess the effectiveness of treatments; (iv) detect malingering; and (v) establish compensation for disability. Frequently, persons who present with complaints of anosmia or hyposmia actually have normal function relative to their peers. Others can be unaware of their deficits. For example, ~90% of patients with idiopathic Parkinson’s disease have demonstrable smell loss, yet <15% are aware of their problem until tested objectively (Doty et al., 1988b).

To meet the need for a modern, practical, clinical olfactory test, in the early 1980s we developed a simple 40-item multiple choice test, the University of Pennsylvania Smell Identification Test (UPSIT). This test, commercially termed the Smell Identification Test™ (Sensonics, Inc., Haddon Heights, NJ; Figure 1), has become the most widely used olfactory test in the world, and can be self-administered by most patients in 10–15 min and scored by non-medical personnel in <1 min (Doty et al., 1984b). Normative data based on results from nearly 4000 people are available (Doty, 1995b), and an individual’s percentile rank can be determined from tables based upon data from normal persons of the same age and gender. Olfactory dysfunction can be classified, on an absolute basis, into one...
of six categories: normosmia, mild microsmia, moderate microsmia, severe microsmia, anosmia and probable malingering. The reliability of this test is high (test–retest Pearson $r > 0.90$) (Doty et al., 1989a). Recently, a shorter version of this test incorporating odorants familiar to a wider range of cultures (the ‘Cross-Cultural Smell Identification Test’ or CC-SIT) has become commercially available (Doty et al., 1996), as has a three-item forced-choice ‘Pocket Smell Test’ designed to replace the simple vials traditionally used by physicians for rough olfactory screening.

### Studies of psychometric properties of olfactory tests

Until our studies, scant attention had been paid to basic psychometric properties of olfactory tests (e.g. reliability and validity), as well as other factors influencing test measures (e.g. intertrial interval). We now know a number of olfactory tests described in the literature are marginally reliable and that comparison of results from these tests with those of more reliable tests in applied settings can lead to false conclusions. An example of this problem can be found in reports, based largely on identical data, that Alzheimer’s disease (AD) is associated with reduced suprathreshold odor identification ability, but not with reduced odor detection threshold ability (Koss et al., 1987, 1988). Unfortunately, this work relied on a small number of patients and an odor detection threshold test too insensitive to pick up a differences between patients and controls—a difference that has been unequivocally documented by nearly a dozen other studies (for reviews see Doty, 1991; Mesholam et al., 1997). This faulty observation has led to the questionable conclusion, now showing up as dogma in some neurology and neuropsychology textbooks, that the olfactory loss in AD is due solely to damage to central integrative mechanisms.

We have performed a number of studies to examine factors that influence odor detection threshold scores. An early study on this topic examined the influences of intertrial interval (ITI) and sniff bottle volume on detection thresholds determined for the rose-like odorant phenyl ethyl alcohol (PEA) using a single staircase procedure (Doty et al., 1986b). While the threshold measures were not significantly influenced by ITIs ranging from 8 to 64 s in the

![Figure 2](https://academic.oup.com/chemse/article-abstract/22/5/565/340007) Detection performance (mean $\pm$ SEM) to phenyl ethyl alcohol diluted in light USP grade mineral oil as a function of reversal number within the staircase series. Reprinted, with permission, from Pierce et al. (1996). © 1996 Perceptual and Motor Skills.

40 subjects evaluated, they did decrease significantly as sniff bottle volume was increased from 65 to 285 ml.

More recently, we completed a study to evaluate the influences of (i) trial sequence position and (ii) diluent type on the PEA threshold value (Pierce et al., 1996). In the first part of this study, detection thresholds were measured in 24 subjects on two test occasions using two different diluents (propylene glycol and USP grade light mineral oil). Threshold values were significantly influenced by diluent type (lower for mineral oil) and trial sequence (lower for later threshold reversals). In the second experiment, 24 subjects were administered a staircase threshold test that involved 15 staircase reversals. Greater numbers of reversals resulted in significantly lowered threshold values (Figure 2). These findings demonstrate the importance of both diluent type and test length with respect to detection threshold values determined by a single staircase procedure, and emphasize a need for standardization of threshold testing procedures.

In 1995 we completed a major effort to establish the reliability of a number of olfactory tests and to determine factors that influence test–retest reliability (Doty et al., 1995). This work represented an extension of our earlier studies on the internal consistency and test–retest reliability of the UPSIT (Doty et al., 1984b, 1985b, 1989a). In this study, 10 tests representing tests of odor identification, detection, discrimination, memory, and suprathreshold odor intensity and pleasantness perception were admin-
istered to 57 subjects on two test occasions. The test–retest reliability and stability of each of 14 test measures derived from these 10 tests was determined. The reliability coefficients of the primary test measures fell into three general ranges bounded by the following \( r \) values: 0.43–0.53; 0.67–0.71; and 0.76–0.90. Detection thresholds were found to be more reliable than recognition thresholds, and staircase threshold procedures were found to be more reliable than single ascending series procedures. A clear relationship was shown between test length and test reliability, and mathematical models were provided to demonstrate such relationships (Figure 3). In the case of the staircase threshold series examined, reliability was related to the number of reversals included in the threshold estimate by a function derived from the Spearman–Brown prophesy formula (Guilford, 1954). Interestingly, reversal location was not strongly related to test–retest reliability. We concluded from this study that (i) olfactory tests differ considerably in terms of reliability; (ii) test length influences reliability in predictable ways; and (iii) differences among olfactory tests administered to the same subjects must be interpreted cautiously.

What do olfactory tests really measure?

Differential reliability is not the only problem associated with inter-test comparisons. Several years ago we administered nine olfactory tests, including tests of odor identification, discrimination, detection, memory, and suprathreshold intensity and pleasantness perception, to 97 healthy subjects and subjected the intercorrelation matrix of 13 measures derived from these tests to principal components analysis (Doty et al., 1994). Four meaningful components emerged; most loaded on the first component. The second component reflected primarily suprathreshold intensity ratings, and the third, mean pleasantness ratings. A response bias measure, derived from a yes/no identification task, loaded most heavily on the fourth component. This study suggests that a number of nominally distinct olfactory tests (e.g. tests of odor detection, memory
and identification) measure, to a large degree, the same component of variance in normal subjects, implying that caution must be taken in assuming that low scores on a given clinical test are due to pathology in the supposed trait or physiological mechanism nominally measured by the test. For example, if a test of ‘odor memory’ is administered to a person whose olfactory neuroepithelium is damaged from age-related cumulative viral insults, the low scores may have little or nothing to do with the neural circuits associated with odor memory per se, yet the prima facia interpretation would be that such circuits are dysfunctional.

Unilateral versus bilateral olfactory testing

Our clinical research, as well as that of others, has found that most disorders of olfactory perception are bilateral (Cain and Rabin, 1989; Doty et al., 1992b). Nevertheless, unilateral problems have been documented (Furukawa et al., 1988), and testing each side of the nose is prudent for the detection of pathology, such as intracranial tumors, that may otherwise go unnoticed until additional diagnostic signs become apparent (Elsberg, 1935). Two years ago, we reported that a decrement observed in unilateral odor memory performance of 24 men and 24 women across a delay interval ranging from 10 to 60 s was mitigated by bilateral testing (Bromley and Doty, 1995), suggesting that some type of central integration may be occurring under bilateral test conditions that facilitates odor memory (Figure 4). This observation extended earlier research on bilateral facilitation of suprathreshold odor intensity (Cain, 1977) and odor identification (Hornung et al., 1990), and suggested the possibility that odor memory may be a common denominator in producing central facilitation.

More recently, we undertook an ambitious project to examine whether PEA odor detection thresholds differed between the two sides of the nose, and if so, whether sex or handedness influenced such measures (S. Betchen and R.L. Doty, submitted for publication). In this work, 30 sinistrals and 132 dextrals were administered a single staircase detection threshold test bilaterally and separately to each side of the nose, with the order of testing being counterbalanced across subjects. In both left- and right-handers, the bilaterally measured thresholds were lower than the thresholds measured on either the left or the right side of the nose. No sex differences were observed, and bilateral thresholds did not differ significantly from the threshold of the better functioning side of the nose. No significant left:right differences were observed in either the left- or the right-handers. This study demonstrates that the bilateral measure likely represents the better functioning side of the nose, a phenomenon observed earlier by Hornung et al. (1990) using a measure of odor identification.

Studies directed at elucidating human odor transduction mechanisms

Several experiments performed at the Center have sought to bring light to events of the human olfactory transduction process. In one study, we sought to determine if a relationship existed between the relative intensity of a number of odorants and their propensity to stimulate adenylate cyclase activity in an in vitro frog ciliary preparation, as well as the magnitude of the electro-olfactogram (EOG) they induced in frogs (Doty et al., 1990). We hypothesized that odorants that induced relatively high levels of such activity should smell stronger than odorants that induce little or no such activity, under the assumptions that (i) olfactory receptors that activate adenylate cyclase are associated with G-protein mediation of olfactory function and (ii) the greater the amount of such activation, the larger the number of transduction elements activated. In the first phase of this study, 10 men and 10 women rank ordered 13 odorants in terms of relative intensity. These rankings were performed five times to stabilize the measures and obtain estimates of test reliability.
The means of the rankings were then correlated with rankings of published measures of odor-induced adenylate cyclase activity in frog cilia (Sklar et al., 1986) and EOG activity in excised bullfrog olfactory epithelia (Lowe et al., 1989). In the second phase of the study, four men and four women provided odor quality dissimilarity ratings among all possible pairs of the stimuli (including AB and BA orders). These ratings were then subjected to multidimensional scaling analysis using the ALSCAL procedure (Carroll and Chang, 1970). These subjects also rank ordered the stimuli in terms of both intensity and pleasantness, and such rankings were correlated, along with the adenylate cyclase and EOG measures, with the derived scale values. This study found that the perceived intensity of the stimuli correlated significantly with both the amount of adenylate cyclase activity induced by the odorants in the ciliary preparation and the magnitude of the EOG, thereby supporting our hypotheses.

Another Center study related to better understanding human olfactory transduction received its impetus from a report of variably decreased olfactory ability in patients with the rare disorder of pseudo-hypoparathyroidism (PHP) (Weinstock et al., 1986). This widely cited report has been used in support of the hypothesis that guanine nucleotide-binding protein (G\(_{s}\)) plays a major role in human olfactory transduction, since PHP Type I patients exhibit deficient stimulatory G\(_{s}\) activity. However, PHP Type Ia patients have other problems that may cause or contribute to olfactory dysfunction, including an unusual constellation of skeletal and developmental deficits termed Albright hereditary osteodystrophy (AHO). Furthermore, it is now known that G\(_{olf}\) is probably the primary G protein involved in olfactory transduction for a number of vertebrates (Nor et al., 1996). For these reasons, we administered the UPSIT, a detection threshold test, and a test of odor memory to 12 patients with Type Ia PHP, eight patients with Type Ib PHP (who had no AHO and reportedly normal olfactory function and G\(_{s}\) protein activity), eight patients with pseudopseudohypoparathyroidism (PHPH; who had a G\(_3\) protein deficiency but no marked insensitivity to parathyroid hormone) and three sets of normal controls matched to these groups on the basis of age, gender and smoking history (Doty et al., 1997b). Although we confirmed that PHP Type Ia patients evidence olfactory dysfunction and that the degree of the dysfunction is greater than that seen in PHP Type Ib, we also found that (i) patients with PHP Type Ib evidence some degree of olfactory dysfunction, (ii) G\(_{s}\) protein-deficient PHPH patients have normal olfactory function and (iii) no meaningful correlations are present between G\(_{s}\) protein activity and any olfactory test measure. These observations throw into question whether olfactory dysfunction associated with PHP is due to generalized G\(_{s}\) protein deficiency, and imply that another G protein deficiency or other mechanisms could be responsible for the olfactory deficits of this disorder.

**Influence of sex and age on olfactory function**

Changes in the ability to perceive odors and tastes are now known to occur with advancing age, are greater in men than in women and can often be quite debilitating. Indeed, a disproportionate number of elderly die from accidental gas poisoning (Chalke et al., 1958) and many complain that food is tasteless (Deems et al., 1991). The latter complaint, which can detrimentally influence interest in food, may explain some cases of age-related nutritional deficiency. It is now well established that decreased 'taste' perception during deglutition largely reflects the loss of stimulation of the olfactory receptors via the retronasal route (Mozell et al., 1969), and we have clearly demonstrated that mouth movements and swallowing have a major impact on such perception, being the retronasal analog to sniffing (Burdach and Doty, 1987). Thus, problems with swallowing and other elements of deglutition experienced by many elderly may contribute to age-related declines in flavor perception. Although it is generally believed that sweet, sour, bitter and salty perception is more resilient to age-related change, in part because of redundancy of innervation of taste buds from several cranial nerves, major age-related alterations are, in fact, observed when small regions of the tongue are tested (Matsuda and Doty, 1995).

Perhaps the first compelling indication of the breadth and magnitude of age- and sex-related changes in olfactory function came from our administration of the UPSIT to nearly 2000 people who spanned a wide age range (Doty et al., 1984a). From this study, it became clear that (i) large individual differences are present in the test scores of older persons; (ii) noticeable olfactory dysfunction is most evident after the sixth decade of life; and (iii) men, on average, evidence age-related declines in odor perception at an earlier age than do women (see Figure 5). This work found
age-related deficits in olfactory function to be profound. Indeed, more than half of the subjects between the ages of 65 and 80 years exhibited major impairment, whereas more than three-quarters of those over the age of 80 years did so. The poor scores of the elderly were not attributable to losses in memory per se, since (i) the memory load on the UPSIT, when administered orally and in a stepwise manner to older persons, does not exceed the span of immediate attention, (ii) UPSIT scores of elderly subjects do not significantly correlate with scores on the Wechsler Memory Scale (Doty et al., 1984b) and (iii) similar losses are observed on two-choice threshold tests where a subject's task is only to report the presence or absence of an odor or to indicate which of two stimuli smells strongest (Deems and Doty, 1987). Age has a much more significant effect on olfactory ability than either gender or smoking, with marked declines seen even in persons who have never smoked cigarettes (Doty et al., 1984a; Frye et al., 1990). The age-related decline and gender difference noted above appear to be universal, as they occur in individuals representing a wide variety of cultures (Doty et al., 1985a). Furthermore, such changes are seen on numerous olfactory tests, including tests of odor detection, identification, discrimination, adaptation and suprathreshold odor intensity perception (Doty, 1992).

Although greater declines in olfactory function can be seen using certain odorants (a phenomenon presumably dependent upon such factors as the odorant's threshold and the nature of the function relating odorant concentration to perceived intensity), declines generally occur for a wide spectrum of odorants. For example, it is now well documented that, in both young and elderly individuals, persons with comparatively low sensitivity to one odorant will typically evidence low sensitivity to others, whereas those who evidence comparatively high sensitivity to an odorant typically evidence high sensitivity to others. With the possible exception of so-called specific anosmias [i.e. decreased ability to detect one or a few compounds in the presence of normal sensitivity to most odorants; see Amoore (1991)], such observations suggest a 'general olfactory acuity' factor exists, analogous to the general intelligence factor derived from items of intelligence tests (Yoshida, 1984; Doty et al., 1994).

Epidemiologic studies of workplace exposure to industrial chemicals on olfactory function

Although sporadic reports of olfactory loss following exposure to environmental chemicals are common (for review see Amoore, 1986), bona fide epidemiologic studies of industrial exposure to well-defined chemicals have been rare. Indeed, we performed the first such study in 1989 (Schwartz et al., 1989) following an earlier feasibility study (Doty et al., 1986a). In this study, we administered the
Figure 6 Effect of cumulative smoking dose on University of Pennsylvania Smell Identification Test (UPSIT) scores for current cigarette smokers. Adjusted UPSIT scores are plotted as a function of the cumulative smoking dose. The linear regression line indicates the magnitude of the smoking dose effect. Note that subjects with very high smoking doses evidence a four-point difference in UPSIT score relative to subjects with low smoking doses. Reprinted, with permission, from Frye et al. (1990). © 1990 American Medical Association.

Figure 7 Effect of cumulative smoking dose and years since cessation from smoking on scores of the University of Pennsylvania Smell Identification Test (UPSIT) for previous cigarette smokers. The individual data were fitted to a distance weighted least-squares regression to derive the surface plot. Although a few subjects evidenced a smoking dose of >70 pack-years, the pack-years scale was limited for clarity of surface illustration. Reprinted, with permission, from Frye et al. (1990). © 1990 American Medical Association.

UPSIT to 731 workers at a chemical facility that manufactured acrylates and methacrylates. In a cross-sectional analysis of the data, no associations of chemical exposure with UPSIT scores were observed. However, a nested case-control study designed to evaluate the effects of cumulative exposure on olfactory function revealed crude exposure odds ratios for the presence of olfactory dysfunction (95% confidence interval) of 2.0 (1.1–3.8) for all exposed workers and 6.0 (1.7–21.5) for exposed workers who had never smoked cigarettes. Logistic regression analysis, adjusting for multiple confounders, revealed exposure odds ratios of 2.8 (1.1–7.0) and 13.5 (2.1–87.6) in these same groups respectively, and a dose–response relationship between olfactory dysfunction and cumulative exposure scores—semi-quantitative indices of lifetime exposure to the acrylates. Thus, exposed smokers were 2.8 times more likely and exposed non-smokers 13.5 times more likely to exhibit olfactory dysfunction than their non-exposed non-smoking counterparts. This study supported observations from histologic studies of the olfactory neuroepithelium of rats that exposure to acrylates can adversely influence the olfactory system.

Pathological influences on olfactory function

A major component of our program is the provision of clinical evaluation, treatment and counseling to patients who suffer from chemosensory disorders. In an extensive study of 750 consecutive patients evaluated at the Center, we found multiple etiologies for chemosensory dysfunction, the three most common being upper respiratory infections, head trauma and nasal sinus disease (Deems et al., 1991). Most patients who presented with complaints of either taste loss alone or both taste and smell loss exhibited meaningful losses only in smell function, as measured by whole-mouth tests (Figure 8). This is due to the fact, mentioned earlier, that decreased 'taste' perception during deglutition largely reflects a loss of stimulation of the olfactory receptors via the retronasal route (Burdach and Doty, 1987).

In addition to studies arising from referred clinical patients, numerous studies have been undertaken to investigate specific medical disorders of interest to our group. Studies performed in the last decade have included blind patients, patients with head trauma (HT), patients with so-called multiple chemical hypersensitivity and patients with a variety of neurodegenerative diseases, including Alzheimer's disease, schizophrenia and various forms of parkinsonism.

Blindness

There has been considerable controversy concerning whether olfactory function is better in visually impaired
Complaints

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Test Results

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<td>0%</td>
</tr>
<tr>
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Figure 8 Distribution of primary chemosensory complaints (left diagram) and test results (right diagram) of 750 consecutive patients evaluated at the Smell and Taste Center. Note that the complaint categories of smell loss, taste loss, and smell and taste loss also include some some patients with secondary complaints of chemosensory distortion and burning mouth. Reprinted, with permission, from Deems et al. (1991). © 1991 American Medical Association.

Persons than in non-visually impaired ones. In the most comprehensive study on this topic to date, we administered the UPSIT and an odor discrimination test to over 50 blind and 75 sighted persons, 23 of the latter being trained members of the water evaluation panel of the Philadelphia Water Department (Smith et al., 1993). In addition, all of the sighted and 39 of the blind were administered a detection threshold test using PEA. The trained sighted subjects outperformed the other groups on odor threshold and discrimination tests, and tended to outperform the other groups on the UPSIT. The scores of the blind subjects did not differ significantly from those of their untrained sighted counterparts. This study reiterates the important role of training with respect to performance on several types of olfactory tests. Blindness per se seems to have no significant influence on such test measures, although presumably blind persons who teach themselves to pay attention to or recognize certain odors would be more adept at tasks involving those odors.

Head trauma

It has long been known that HT can adversely affect the ability to smell (for review see Costanzo et al., 1995). As demonstrated in extensive magnetic resonance imaging (MRI) studies of HT victims presenting to the Center with complaints of olfactory dysfunction, damage to the olfactory bulbs, tracts, and frontal and temporal poles is evident on appropriate MRI imaging (Yousem et al., 1996; Doty et al., 1997d). Pathologically, filaments of the CN I that pass through the cribriform plate are damaged by coup/contra-coup movement of the brain. Following such damage, distal sectors of the axons degenerate. Ingestion of axon fragments by macrophages derived from blood monocytes follows a period of inflammation. Schwann cells, some of which receive fibers from surviving axon stumps, proliferate within the surviving elements of the basement membrane. Cellular changes indicative of decreased protein synthesis occur within several weeks of nerve severance, including migration of nuclei to the periphery, enlargement of cell bodies and proliferation of Nissl substance. The degree of degeneration depends upon the number of axons severed and the degree to which endoneural sheaths are preserved. Unfortunately, in adult humans extensive CN I fiber regeneration seems to be rare, presumably because of the formation of collagenous scar tissue that inhibits passage of olfactory axons through the cribriform plate (Moran et al., 1992) and the lack of adequate trophic factors within the damaged olfactory bulbs and tracts. Regeneration, when present, takes months (Schultz, 1960).

In the aforementioned evaluation of 750 consecutive patients of our clinic, HT was among the most common causes of olfactory loss. Indeed, only upper respiratory infections and nasal sinus disease accounted for more patients. Recently, we examined scores on the UPSIT, the Beck Depression Inventory (BDI), and items from a detailed medical health and history questionnaire of 268 patients who had entered the Center with complaints of HT-related olfactory dysfunction (Doty et al., 1997d). Sixty-six of these patients were retested after various test–retest periods ranging from 1 month to 13 years. The volumes of olfactory-related brain structures (bulbs, tracts and temporal lobes) of 15 patients were quantified using high resolution MRI in a manner performed in an earlier, more extensive, study (Yousem et al., 1996). Sixty-six percent of the patients were found to be anosmic, 20% microsmic and 13% normosmic. Frontal impacts produced less dysfunction than side or back impacts. On retest, 36% of the patients had improved slightly, 45% had not changed and 18% had worsened; only three patients, none of whom was initially anosmic, regained normal function. Trauma severity was related to olfactory test scores in microsmic patients, and parosmia prevalence decreased from 41.1% to 15.4% over an 8 year post-trauma period. Interestingly, the olfactory bulb/tract volumes of male, but not female, HT patients were greatly reduced relative to controls, presumably reflecting
the greater average trauma severity of the males. Overall, this study found that (i) patients complaining of HT-related olfactory dysfunction are typically anosmic and rarely regain their normal ability to smell; (ii) parosmia prevalence decreases over time in such patients; and (iii) damage to olfactory eloquent brain structures can be observed in most such cases using an appropriate MRI protocol.

Multiple chemical hypersensitivity
There has been considerable controversy regarding claims of heightened olfactory sensitivity in patients who report diffuse symptoms related to apparent repeated exposure to environmental chemicals (the so-called multiple chemical hypersensitivity syndrome, or MCS). However, until a study was performed at our Center in 1988, no scientific studies on the influence of MCS on olfactory function had been performed. To remedy this situation, we measured odor detection thresholds to PEA and to methyl ethyl ketone in 18 MCS patients and 18 matched controls; in addition, we assessed depression and a number of autonomic system-related variables, including blood pressure, heart rate, respiration rate and nasal resistance (Doty et al., 1988a). Although the detection thresholds of the MCS patients did not differ significantly from those of the controls, the MCS patients did exhibit higher levels of depression and odor-related increases in nasal resistance and respiration rate, suggesting that MCS is associated with autonomic and psychologic factors.

Neurodegenerative diseases
Among the more interesting cases of olfactory dysfunction are those associated with some forms of neurodegenerative disease. As described in detail below, our studies indicate that such dysfunction (i) is not uniform among all neurodegenerative disorders in either magnitude or frequency, (ii) appears to be among the first (if not the first) signs of AD, idiopathic Parkinson's disease (PD) and the parkinsonism-dementia complex of Guam (PDC), (iii) appears to be of the same frequency and magnitude in AD, PD and PDC, and (iv) differentiates between the closely related and often confused neurodegenerative disorders of PD and progressive supranuclear palsy (PSP). Furthermore, we now have evidence that the olfactory loss observed in multiple sclerosis (MS) is proportional to the number of MS-related plaques within central brain regions associated with higher-order olfactory processing. For these and other reasons, studies of olfactory dysfunction in patients with neurodegenerative disorders has remained a major element of our Center's olfactory research program.

Alzheimer's disease
In our first study of a neurodegenerative disorder, both the UPSIT and an odor detection threshold test were administered to 34 patients with probable AD, an insidious progressive brain syndrome associated with global deterioration of cognitive function and severe social impairment (Doty et al., 1987). We clearly demonstrated that decrements on both types of tests are present in the majority of patients with this disorder relative to age- and sex-matched normal controls (Figure 9). This work, along with a number of other studies, has clearly established that olfactory dysfunction is present in early AD, and that such dysfunction can be assessed using tests of identification, detection, discrimination and memory (for review see Doty, 1991). Although aspects of the dysfunction seen in AD may be associated with the aging process per se, early-stage AD patients with mild dementia consistently score much more poorly on olfactory tests than do age-matched controls (Doty et al., 1987). Even the three-item Pocket Smell Test

![Figure 9](https://academic.oup.com/chemse/article-abstract/22/5/565/340007/0601007)
allows for a clear differentiation between patients with AD and age-matched patients with major depression (Solomon et al., 1997). Despite the fact that several studies have reported the magnitude of the olfactory dysfunction to be weakly related (rs typically <0.40) to dementia severity (Waldton, 1974; Richard and Bizzini, 1981; Corwin and Serby, 1985; Knupfer and Spiegel, 1986; Murphy et al., 1990), obvious problems exist in interpreting psychophysical data from demented persons, making such test results enigmatic.

**Amyotrophic lateral sclerosis**

Amyotrophic lateral sclerosis (ALS), unlike AD, is a disorder in which widespread denervation of upper and lower motor neurons, but not central brain tissue, occurs (Kuncl et al., 1997). As in AD, the clinical diagnosis is one of exclusion, and little racial or geographic variation has been found in the incidence of ALS within or among countries (Kurtzke, 1982). Traditionally, the assumption has been made that ALS is not associated with alterations in any of the primary senses, aside from those mediated via afflicted peripheral nerves.

Recently we made the exciting discovery that ALS is accompanied, at least in some individuals, by discernible deficits in olfactory perception which seem to correlate with electrophysiological indices of peripheral nerve function (Sajjadian et al., 1994). In this study, we administered the UPSIT bilaterally to 17 female and 20 male, and unilaterally to seven male and seven female ALS patients. Age-, gender-, smoking habit- and race-matched controls were also tested. The ALS patients exhibited significantly lower average UPSIT scores than did the controls (~30 versus ~35). Of the 37 ALS patients, 28 (i.e. 75.7%) had UPSITs scores below those of their matched controls, although, on average, the degree of dysfunction was not as great as that seen earlier in patients with AD, PD and the PDC of Guam. Only four (11%) of the ALS patients had UPSIT scores indicative of total or near total anosmia. The UPSIT scores of the ALS and control subjects decreased as a function of age, and no sex differences or laterality in the ALS-related test scores were observed.

**Down's Syndrome**

Adults with Down's Syndrome (DS), particularly those that live beyond three decades, exhibit neuritic plaques and neurofibrillary tangles (NFTs) analogous to those observed in AD. While the appearance of significant numbers of NFTs is usually delayed until the third decade of life, increased deposition of amyloid in the form of senile plaques or diffuse amyloid deposits occurs in the entorhinal cortex as early as 19 years of age (Hof et al., 1992). It is of interest that several studies, including ones using the UPSIT, have reported that adult DS patients have difficulty smelling (Warner et al., 1988; Hemdal et al., 1993; Zucco and Negrin, 1994). Unfortunately, all but one of these studies failed to compare the DS test scores to scores from non-DS retarded control subjects, making it conceivable that the observed deficits were due to mental retardation rather than DS per se. The sole study that controlled for this possibility found that 20 adult DS subjects (mean age = 23.1 years) scored more poorly on a modified version of the UPSIT and a yes/no odor identification test than did 15 idiopathic mentally retarded controls matched to the DS subjects on the basis of IQ (Hemdal et al., 1993).

Given the close association between AD and smell dysfunction, we sought to determine if 20 young adolescents with DS (mean age = 13.9 years) had UPSIT or odor discrimination test scores that differed significantly from 20 mentally retarded and 20 non-mentally retarded controls matched on the basis of IQ (McKeown et al., 1996). No significant differences were observed, suggesting that DS-related olfactory dysfunction, if present in DS, delays its appearance until the age when AD-like pathology is present.

**Essential tremor**

Essential tremor (ET) is an idiopathic tremor that is frequently progressive and exaggerated by action and emotional tension. At least some studies have suggested that ET is associated with PD (Geraghty et al., 1985; Cleeves et al., 1988). Recently, the UPSIT was administered to 16 patients with ET, 16 patients with PD and 16 normal controls (Busenbark et al., 1992). The test scores of the ET patients did not differ significantly from those of the controls, unlike the test scores of the PD patients, which evidenced a significant decrease (respective UPSIT means: 37.2, 36.3 and 27.4; see PD section below). Thus, ET and PD differ with regard to olfactory function, suggesting that olfactory testing may be of value in the differential diagnosis of these two conditions.

**Huntington's disease**

Although it has been known for over a decade that patients with Huntington's disease (HD) exhibit olfactory dysfunction (Moberg et al., 1987), only recently has the
question been posed as to whether olfactory dysfunction may be an early marker of this disorder. In the first study on this topic, we administered the UPSIT and an odor detection threshold test to 25 probands with HD, 12 at-risk offspring (four of whom subsequently developed HD) and 37 unrelated controls (Moberg and Doty, 1997). The HD patients exhibited significant impairment on both measures of olfactory function, unlike the controls and at-risk offspring, who did not differ from one another, implying that the olfactory dysfunction is present only at the time of the expression of the motoric signs of the disorder. More recently, we confirmed these findings in 20 affected HD patients, 20 neurologically normal individuals who carry the genetic mutation at IT15 which causes HD and 20 neurologically normal individuals who do not carry this mutation (Blysma et al., 1997).

Korsakoff's psychosis
A number of earlier studies had suggested that Korsakoff's psychosis, a disorder in which punctate lesions within the mamillary bodies and sectors of the thalamus are documented following long-term thiamine deficiency, is associated with decreased ability to smell (e.g. Gregson et al., 1981). Robert Mair, William McEntee and I documented such loss using the UPSIT (Mair et al., 1986). Interestingly, using stepwise multiple regression, we found a strong association between UPSIT scores and CSF levels of the noradrenergic metabolite, 3-methoxy-4-hydroxy-phenyl glycol (MHPG; \( r = 0.87, P < 0.002 \)).

Multiple sclerosis
Because the primary olfactory neurons are unmyelinated in multiple sclerosis (MS), it has been assumed by a number of authors that the olfactory system is preserved in this common neurological disorder (e.g. Lumsden, 1970). Indeed, early psychophysical studies, including the pioneering one of Anasari (1976), found no olfactory deficits in patients with this disorder. Even a comparatively recent study by Kesslack et al. (1988), which administered the UPSIT and a match-to-sample test to 14 MS patients, reported no deficits.

In contrast to such studies, we found, in 1984, that 23% of the 31 MS patients we evaluated evidenced some degree of olfactory dysfunction on the UPSIT (Doty et al., 1984b). More recently, we presented case studies in which olfactory dysfunction was the presenting symptom of MS (Constantinescu et al., 1994). This year, we used high-resolution MRI to quantify the number and location of MS-related plaques within the brain of 26 patients with MS (Doty et al., 1997c). Although the total number of brain plaques did not correlate with UPSIT scores, the number of plaques found in olfactory eloquent structures—the temporal lobes and regions of the frontal cortex—did correlate. Indeed, a very high correlation \( r = -0.94 \) was observed between UPSIT scores and the number of plaques found in these areas (Figure 10). No such relationship was present between the UPSIT scores and plaques in other brain regions (Figure 11). Clearly, an olfactory loss in MS depends directly upon the presence of plaques within cortical brain regions associated with the olfactory system.

Parkinson's disease
James Parkinson, in his classic monograph on shaking palsy for which he is now known (Parkinson, 1817), defined this palsy as 'Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured'. Until relatively recently, PD was still believed, in accord with Parkinson's view, to be unaccompanied by sensory changes. Today the diagnosis of PD is still solely based on the presence of a set or subset of cardinal motoric signs (e.g. rigidity, bradykinesia, tremor and postural reflex disturbance).

We now know that olfactory dysfunction is very common...
in PD patients. Indeed, the proportion of early-stage PD patients with olfactory dysfunction appears to be greater than the proportion of early-stage PD patients exhibiting any one of the cardinal signs of PD (i.e. tremor, rigidity, bradykinesia or gait disturbance). We found, in 1988, that 73 of 81 patients studied (90%) had odor identification test scores lower than their matched normal controls, and 29 of 38 patients studied (76%) had higher olfactory thresholds than matched controls (Doty et al., 1988b). On average, PD patients scored ~20 on the UPSIT (Figure 12). Subsequently, we demonstrated definitively that the deficit is bilateral (Doty et al., 1992b), present in early hemiparkinsonism (Doty et al., 1988b), stable over time (Doty et al., 1988b) and unrelated to disease stage (Doty et al., 1988b), degree of motoric symptomatology (Doty et al., 1988b, 1989b) or use of antiparkinson medications (Doty et al., 1988b), in accord with some of the findings of others (Ward et al., 1983; Quinn et al., 1987; Bromley and Doty, 1995).

Recently we have found evidence that subtle variations may exist among some subtypes of PD when large numbers of PD subjects are evaluated (Stern et al., 1994). For example, 80 patients with ‘benign PD’ (where the disease has been confined to Hoehn & Yahr Stages I or II for at least 4 years) were found to evidence a higher average UPSIT score (mean = 22.51, SD = 8.5) than 29 patients with ‘malignant PD’ (Hoehn & Yahr Stage III) (mean = 17.38, SD = 6.29). Twenty-two patients with chronic hemiparkinsonism (uni-

![Figure 11](https://academic.oup.com/chemse/article-abstract/22/5/565/340007/577)  

Figure 11 Scores on the University of Pennsylvania Smell Identification Test (UPSIT) as a function of the number of plaques counted in brain regions other than the inferior temporal and frontal lobe regions of 26 patients with multiple sclerosis (MS). Note lack of association between the two measures. Reprinted, with permission, from Doty et al. (1997). © 1997 Massachusetts Medical Society.

lateral signs for 4 or more years) evidenced a higher UPSIT score than 96 patients with bilateral parkinsonism [respective mean UPSIT (SD) scores: 24.36 (8.45) versus 20.42 (7.94)]. In general, the more malignant subtype of PD, the greater the olfactory dysfunction.

**Parkinsonism–dementia of Guam**

Amyotrophic lateral sclerosis, parkinsonism and dementia accounted for at least 15% of adult deaths among the Chamorro populations of Guam and Rota between 1957 and 1965 (Reed and Brody, 1975; Reed et al., 1966). A genetic or infectious cause of these disorders has not been established from epidemiologic studies, including case control comparisons and extensive pedigree analyses.

We administered the UPSIT to 24 Guamanians with early signs of PD and compared their test scores to those of age- and gender-matched North American patients with early-stage AD and early-stage PD (Doty et al., 1991). No differences were observed between the test scores of the three groups, suggesting that the olfactory dysfunction observed in these three disorders may reflect a common neurologic substrate. Although the specific substrate is unknown, it has been documented that the anterior olfactory nucleus of these patients is nearly void of neurons (D.P. Perl and R.L. Doty, unpublished data; Figure 13).

**Progressive supranuclear palsy**

The Steele, Richardson and Olszewski syndrome, better known as PSP, accounts for nearly 5% of patients with parkinsonian symptoms (Jankovic, 1989). On its initial
Figure 13  Number of neurons within the anterior olfactory nucleus of four patients with the Parkinson-dementia complex (PDC) of Guam and seven normal controls as a function of age. Note the decline in the number of neurons within the anterior olfactory nucleus as a function of age and the virtual absence of neurons within this structure of patients with PDC (D. Perl and R.L. Doty, unpublished data).

presentation, this disorder is commonly characterized by rigidity and bradykinesia; tremor is rarely present. Vertical-gaze paresis and a slowing of thought processes are among the most distinguishing features of PSP (Steele et al., 1964). PSP is often misdiagnosed as PD, since it shares a number of motor symptoms with PD. However, it is less responsive to anti-PD medications (Jackson et al., 1983) and usually exhibits comparatively more severe frontal lobe dysfunction (Cambier et al., 1985), more neuronal loss within the basal ganglia and the upper brain stem (Jankovic, 1989), and less damage to the mesolimbic and mesocortical dopamine systems than PD (Ruberg et al., 1985).

We have recently demonstrated that, unlike PD patients, patients with PSP have a relatively normal sense of smell (Sajjadian et al., 1994). Twenty-one PSP patients and 21 matched controls were administered the UPSIT; 17 patients and 17 controls were also administered a PEA single staircase forced-choice odor detection threshold test (Doty et al., 1986b). In contrast to the olfactory test scores of the PD patients, the PSP test scores did not differ significantly from those of the controls, suggesting that olfactory testing may be useful in the differential diagnosis of these diseases.

Schizophrenia
There is now clear evidence that olfactory function is severely damaged in schizophrenia. Deficits in odor identification (Hurwitz et al., 1988; Serby et al., 1990; Houlihan et al., 1994), odor detection threshold sensitivity (Geddes et al., 1991) and odor memory (Moberg et al., 1987; Wu et al., 1993) have all been reported. Several studies have reported that men with schizophrenia evidence lower UPSIT scores than women with schizophrenia (Hurwitz et al., 1988; Kopala et al., 1989; Kopala and Clark, 1990; Kopala et al., 1992). Although this suggests the possibility of an X-linked inheritance, several studies by our group have not replicated this sex effect (Moberg et al., 1997a). In one study we administered the UPSIT to 16 elderly patients who met DSM-III-R criteria for schizophrenia, 20 patients with NINCDS–ADRDA diagnosis of probable AD and 20 healthy elderly controls. The UPSIT scores of both the AD and schizophrenia patients, which did not differ significantly from one another, were markedly depressed relative to the normal controls. In another study, we administered the UPSIT to 38 patients with well-defined schizophrenia and 40 controls (Moberg et al., 1997b). As in our earlier study, an ANOVA revealed no sex difference, but a clear schizophrenia-related deficit emerged. Importantly, duration of illness was correlated (r = -0.92, P < 0.001) with UPSIT performance (Figure 14). This latter finding has received considerable attention in the neuropsychological community, since it is the only neuropsychological marker identified, to date, associated with disease duration and, thus, presumably disease progression.

The olfactory vector hypothesis of neurodegenerative disorders

Although the physiological basis for the olfactory dysfunction of at least one neurodegenerative disorder, MS, has been elucidated (Doty et al., 1997c), a physiological basis for the olfactory loss in other neurodegenerative disorders is obscure, largely because of widespread alterations in numerous brain regions and neurotransmitter systems. Similarly, the etiology of most neurodegenerative disorders is unknown. Although viruses and environmental factors have been implicated in the etiology of several neurodegenerative disorders (e.g. encephalitis lethargica- and MPTP-induced parkinsonism), the relative contributions of environmental and genetic predispositional factors are not clear. One of the more interesting and controversial theories proposed to explain both olfactory losses and the etiology of disease process in several neurologic diseases is the 'olfactory vector hypothesis' (OVH) (Pearson et al., 1985; Ferreyra-Moyano and Barragan, 1989; Harrison, 1990). A basic tenet of this hypothesis is that olfactory
dysfunction results, directly or indirectly, from damage to the olfactory pathway as a result of the transit of an environmental virus, toxin or other xenobiotic agent from the nasal cavity into the brain via the olfactory fila (Roberts, 1986; Ferreyra-Moyano and Barragan, 1989; Doty, 1991). Such a hypothesis follows from the fact that the olfactory receptor cells, whose cilia and dendrites in the human have a combined surface area of ~9 sq. in. (Doty, 1997), are in direct contact with the external environment. These cells serve as both the receptor cell and first order neuron, projecting an axon directly into the brain without any intervening synapses.

The propensity for agents to move from the nasal cavity into the brain via the olfactory nerves or surrounding mucosa has been known for many years. Indeed, Claudius Galen alluded to the permeability of the dura matter around the cribriform plate to both water and air in the second century AD, and propagated an ancient theory, which was widely accepted until the nineteenth century, that agents responsible for olfactory sensations pass through the foramina of the cribriform plate into the ventricles of the brain (Wright, 1914; Doty, 1995a). Scientific studies confirmed the movement of materials from the nasal cavity into the brain in the eighteenth and nineteenth centuries, and demonstrated, in the early twentieth century, that agents responsible for olfactory sensations pass through the cribriform plate into the ventricles of the brain (Wright, 1914; Doty, 1995a). 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The invariable finding of severe and even maximal involvement of the olfactory regions in Alzheimer's disease is in striking contrast to the minimal pathology in the visual and sensorimotor areas of the cortex and cannot be without significance. In the olfactory system, the sites that are affected—the anterior olfactory nucleus, the uncus, and the medial group of amygdaloid nuclei—all receive fibers directly from the olfactory bulb. These observations at least raise the possibility that the olfactory pathway is the site of initial involvement of the disease.

Circumstantial support for the OVH in producing the olfactory loss of PD comes from evidence that (i) certain viruses and toxins (e.g. carbon disulfide, manganese and encephalitis lethargica) have been epidemiologically associated with PD (von Economo, 1931; Eadie et al., 1965); (ii) such agents can readily enter the CNS via the primary olfactory neurons (Stroop, 1995); and (iii) patients whose parkinsonism is due to i.v. injection of the proneurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) have relatively normal smell ability (Doty et al., 1992a), an expected result since the toxicant did not enter the CNS via the olfactory fila. In PD, the magnitude of olfactory loss bears little or no relation to the degree of motor or cognitive symptoms (implying independence from the more dynamic elements of the disease proper), is uninfluenced by antiparkinsonian medications (e.g. L-DOPA) (Doty et al., 1992b), and does not progress significantly over time (Doty et al., 1989b)—phenomena that would be expected if irreversible damage had been done to segments of the olfactory pathway early in the disease process. As noted earlier, the olfactory deficit of PD appears to be indistinguishable from that of AD (Doty et al., 1991), suggesting

![Figure 14](https://example.com/figure14.png)

**Figure 14** Age- and gender-adjusted University of Pennsylvania Smell Identification Test (UPSIT) scores as a function of duration of illness in schizophrenia. Reprinted, with permission, from Moberg et al. (1997b).
the possibility that the deficit of these two disorders may share a common neuropathological substrate.

Despite its intuitive appeal, a number of theorists have argued that the olfactory vector hypothesis is an unlikely explanation, particularly in AD, for either the olfactory loss or the induction of the disease in question (see Harrison, 1990). Most such arguments focus on the apparent pattern of degeneration within the brain. It has been pointed out that the direction of the progression of damage (i.e. formation of plaques and tangles) in AD seems to be from more central structures outward, in contradiction to what one might expect if an agent entered the nose and produced damage en passant. Mann (1989), for example, was among the first to argue that AD-related degeneration begins in cortical, not subcortical, brain regions, pointing out that the major subcortical nuclei altered in AD (i.e. nucleus basalis, locus coeruleus and dorsal raphe) project to common cortical areas, whereas subcortical nuclei that do not project to such areas are unaltered. He also pointed out that the AD-related cell loss observed in the locus coeruleus is confined to its dorsal sectors (which project to cortical regions), rather than to its ventral sectors (which project to the spinal cord, basal ganglia and cerebellum). Elsewhere, Mann et al. (1988) argue that, because the frequency of plaques and tangles is lower in the olfactory bulb and tract than in the amygdala and hippocampus, the direction of damage must be central to peripheral:

As they stand these data imply that the olfactory bulbs are affected later in the course of the ‘disease’, perhaps as a retrograde spreading out of change from the amygdala and hippocampus and that the olfactory pathways do not, as suggested by Pearson et al., provide a portal of entry to the brain for the ‘Alzheimer pathogen’. However, it is still possible that the formation of SP [senile plaques] and NFT [neurofibrillary tangles] within the amygdala and hippocampus results from other processes (e.g. a defect in blood brain barrier function) in which areas which are ‘triggered off’ by a pathogenic agent spread via the olfactory pathways. If this were to be so formation of NFT in neurones of the olfactory nuclei would not occur during orthograde transport of such an agent but would result from a later retrograde reaction; as such the lesser degree of SP and NFT formation within the olfactory bulb and tracts would be expected.

Further support for the spread of AD pathology from central to peripheral areas comes from an autopsy study of brains from 100 AD patients (Okamoto et al., 1990). Plaques were found in the olfactory bulbs, including the anterior olfactory nucleus, tufted and mitral cells, only in cases where larger numbers of plaques were present in the cerebral cortex, implying that the olfactory bulbs are not the earliest sites of plaque formation. In addition, Vogt et al. (1990) point out that sectors of the amygdala receiving olfactory projections appear not to be those which are most reliably laden with plaques and tangles.

Additional arguments that have been made against the olfactory vector hypothesis include (i) the fact that familial forms of AD are known; (ii) AD-like pathology inevitably occurs in older persons with DS (Rebeck and Hyman, 1993), implying a genetic basis for the disorder; and (iii) plaques and tangles have been demonstrated in a standard AD-like distribution in a 65-year-old anosmic, non-demented woman with an imperforate cribriform plate, rudimentary olfactory bulbs/tracts and sulcal abnormalities of the orbitofrontal region (Arriagada et al., 1991).

While such arguments certainly limit aspects of the olfactory vector hypothesis in AD, particularly the notion of a 1:1 correspondence between neural degeneration and movement of a virus or toxicant through the olfactory pathway, they do not invalidate the idea that agents responsible for both smell loss and disease genesis make their way into the CNS via the olfactory fila. As alluded to by Mann et al. (1988), above, viruses or other agents that enter the CNS via the olfactory fila could selectively damage more central regions of the limbic system, beginning with the most vulnerable areas [e.g. highly vascularized central brain regions (see Bell and Ball, 1990)] and subsequently produce a central-to-peripheral propagation of damage. Importantly, neuroperventil virul and viral excitability is well documented. For example, Barnett et al. (1993) employed in situ hybridization to compare the spread of two viruses, herpes simplex virus type I and mouse hepatitis virus strain JHM, through the olfactory pathways. While both viruses entered the brain via the olfactory system, only one—herpes simplex—infected noradrenergic neurons in the locus coeruleus. Despite the fact that both viruses infected dopaminergic neurons in the ventral tegmental area, mouse hepatitis virus produced much more widespread infection. Such observations, which reflect only a small sample of the vast literature on selective damage from viruses that can invade the CNS via the olfactory pathways, emphasize the fact that the pattern of neuropathologic markers within the brain, such as plaques and tangles, need not reflect the
specific direction or routes of passage of an offending agent through the CNS.

Genetic determinants of AD-like pathology, as is likely in DS, do not have to be incompatible with the olfactory vector hypothesis. For example, one can envision genetically determined protection mechanisms within the olfactory neuroepithelium, such as the cytochrome P-450 enzyme system (Gresham et al., 1993), which become compromised at some stage of the disease process, allowing for entry or improper protection against an exogenous agent that induces the sensory dysfunction. In accord with such a view is the epidemiological observation that tobacco smokers have reduced risk of contracting AD and PD (Tanner, 1991). Cigarette smoke contains high levels (100–250 ng/cigarette) of polycyclic aromatic hydrocarbons (PAHs) that serve as inducers of cytochrome P-450 enzyme systems (Anonymous, 1989). Stimulation of such enzymes leads to increased metabolism of xenobiotics within the olfactory epithelium (as well as within the liver), thereby conceivably preventing environmental neurotoxins from reaching target organs (Gresham et al., 1993). Such a process would account for our finding that smokers are at lower risk for reduced olfactory function than non-smokers from exposure to methacrylates, acrylates and acetone (Schwartz et al., 1989, 1990).

It is widely believed that AD has more than one etiology. Thus, an autopsy case in which the cribriform plate seems imperforate and NFTs are distributed within brain structures in a typical manner could reflect the entry of an offending agent through an alternative route, but does not invalidate the general hypothesis that many, if not most, cases of AD could be caused by agents that enter the CNS via the olfactory pathways. Obviously, in such an example an olfactory loss would be unlikely to be due to an agent entering the brain via the cribriform plate.

Regardless of the validity of portions or all aspects of the OVH, it is clear that olfactory loss is not uniform among neurodegenerative disorders. Clearly, an explication of both the distal and proximal determinants of olfactory loss in a wide range of neurodegenerative disorders warrants additional study.

**Summary**

In this presentation, I have reviewed a number of studies from the Smell and Taste Center's human psychophysical and clinical programs. Some of these programs were designed to develop accurate means for assessing human olfactory function and to apply the developed instruments to a number of subject and patient groups. As can be seen in the information presented this afternoon, we have made considerable progress to this end. Another goal of our work has been to ascertain the basis for the olfactory loss of selected neurodegenerative disorders. Although we are still avidly working towards this goal, we have made considerable progress along the way, demonstrating, among other things, that the olfactory loss of MS is due to discrete foci of inflammation and degeneration within central brain structures. Importantly, we have shown that many factors alter the ability to smell, and that careful psychophysical measurement can accurately assess the extent of such influences. Presently, we are expanding our human program into a number of areas, including the evaluation of odor-induced evoked potentials and changes in brain metabolism and activity measured by positron emission tomography and functional magnetic resonance imaging. Clearly, the task at hand will be to explain the neuro-anatomical and neurochemical bases for the olfactory losses observed in a wide range of neurological disorders.

We owe much of our insight to the intellectual olfactory heritage of Utrecht University, and wish EP the very best of luck in this new stage of his career. I thank Jan Kroeze, Professor Köster and the members of the organizing committee for their efforts and providing me with the honor of talking to you this afternoon.

**ACKNOWLEDGEMENTS**

This paper is based on an invited talk presented at a symposium held in honor of Professor E.P. Köster's retirement from Utrecht University. The paper was presented at the Academiegebouw in Utrecht, Netherlands, on October 22, 1995. Supported by National Institute on Deafness and Other Communication Disorders Grant PO1 DC 00161, National Institutes of Health.
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Received and accepted on July 21, 1997