stimulated cells. However, cells stimulated in the presence of CsA were negative for this band and did not show any hybridization (Fig. 2).

The combination of biological and chemical measurements for IL-2 mRNA makes it extremely unlikely that IL-2 mRNA was present in the CsA-inhibited cells in any form. We conclude that the accumulation of IL-2 mRNA seen after stimulation of Jurkat or EL4 cells is blocked by CsA. The applicability of these studies to normal human or murine lymphocytes must be confirmed by further experiments. It is important to note, however, that the effect of CsA on the production of IL-2 noted here with these tumor cell lines occurred at the same concentrations as with normal murine splenic lymphocytes stimulated with Con A (*2*). The CsA effect could be mediated by inhibition of IL-2 mRNA transcription or by its destabilization. It was recently shown that insulin selectively inhibits synthesis of mRNA for the enzyme phosphoenolpyruvate carboxykinase in a cell line (*14*); the present results would be explained if a similar inhibition of IL-2 mRNA synthesis were caused by CsA. In summary, it appears that at least part of the immunosuppressive activity of CsA is due to its ability to selectively inhibit accumulation of mRNA coding for IL-2 in human and murine T lymphocytes.

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Smell Identification Ability: Changes with Age

Abstract. *Smell identification ability was measured in 1955 persons ranging in age from 5 to 99 years. On the average, women outperformed men at all ages, and nonsmokers outperformed smokers. Peak performance occurred in the third through fifth decades and declined markedly after the seventh. More than half of those 65 to 80 years old evidenced major olfactory impairment. After 80 years, more than three-quarters evidenced major impairment. Given these findings, it is not surprising that many elderly persons complain that food lacks flavor and that the elderly account for a disproportionate number of accidental gas poisoning cases each year.*

The human sense of smell serves as an early warning system for the detection of fire, dangerous fumes, and polluted environments, and it largely determines the flavor and palatability of foods and beverages (1). Despite these important functions, the nature and degree of age-related changes in this sense are unknown. Practical considerations of stimulus presentation and control have limited human olfactory studies to only a few odorants and relatively small numbers of "young" and "old" subjects (unlike studies of vision and audition, where standardized tests have been administered to thousands of subjects of all ages). Although most olfactory threshold studies report higher thresholds in older than in younger subjects (*2*), some have not found age-related changes (*3*), and suprathreshold data on this topic are contradictory (*4*). As indicated in one recent review, "Most assume that aging is correlated with decreased ability in all sense modalities. Actually, the effect of aging on odor perception is not clear and has been debated since the beginning of this century" (*5*).

To date, no systematic evaluation of smell function has been performed across the entire age span. However, the recent development of a rapidly administered microencapsulated test of olfactory function has now made it possible to accurately assess the odor identification ability of large numbers of subjects in a standardized manner (*6*). Unlike detection threshold measures, this 40-odorant forced-choice test is sensitive to a broad range of olfactory deficits, including odor recognition problems originating in the central nervous system (*7*).

We now report, in a study of 1955 persons ranging in age from 5 to 99 years, that (i) average ability to identify odors reaches a peak in the third and fourth decades of life (between 20 and 40 years) and begins to decline monotonically after this time, (ii) a large proportion of elderly persons are anosmic, (iii) smoking has an adverse effect on odor identification ability, and (iv) women of all ages are generally more accurate than their male counterparts in identifying odors.

The subjects consisted of (i) employees of the University of Pennsylvania, (ii) residents of homes for the elderly, (iii) persons attending regional health fairs and other public events, (iv) university students, (v) primary and secondary grade school students, and (vi) youngsters enrolled at summer camps (*8*). Although the majority self-administered the test under our supervision, we administered it individually to many of the children and most of the elderly. In these instances, the response alternatives were read to the subjects before and during the sampling of each stimulus.

The sample quartiles for each decade are shown in Fig. 1. For the second through fifth decades, the data were modified according to a Box-Cox transformation, and a normal distribution was fit to the transformed values (*9*). For these decades the quartiles were calculated from the fitted normal distributions and then converted to the original scale of measurement.

A weighted least-squares multiple regression analysis revealed that age, gender, current smoking habits, and being a resident in a home for the elderly were significantly related to the test scores (*10*). On the average, women outperformed men at all ages (Fig. 1). Peak performance was achieved by both sexes during the third through fifth decades, followed by a slight decrease in average performance across the sixth and seventh decades and a marked decrease

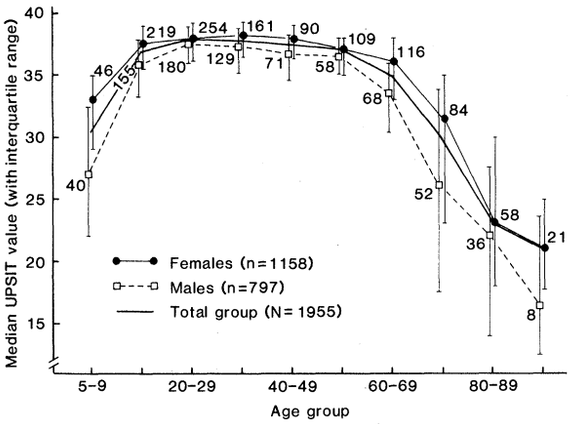

Fig. 1. University of Pennsylvania Smell Identification Test (UPSIT) scores as a function of age and gender. Numbers by data points indicate sample sizes.

after the seventh (*11*). That this drop is unlikely the result of changes in memory, per se, is suggested by a study of 47 elderly subjects, whose scores on this test were not significantly correlated with those on the Wechsler Memory Scale (even though, individually, each of these measures was negatively correlated with age) (*12*).

The changes in smell identification scores with age resemble changes seen in perceptual measures from several other major sensory systems. For example, peak performance occurs in a number of measures of visual and auditory function in the third and fourth decades of life, with subsequent declines commonly following the general pattern seen in Fig. 1 (*13–15*). A comparison of the present data with those from suprathreshold measures of vision and hearing is presented in Fig. 2. Despite the likelihood of different physiological bases for these changes, the quality of suprathreshold sensory perception diminishes similarly in these three senses in the later years. This is not surprising if one views the senses functionally as interactive systems for extracting environmental information, rather than as solely independent entities (*16*).

Although superior female performance has been noted in a number of earlier odor identification studies (*17*), the present results reveal that the sex difference is present within all age categories, including prepubertal ones. This finding is in accord with reports that prepubertal girls outperform prepubertal boys on a number of odor detection tasks (*18*), and throws into question the widely held notion that sex differences in olfactory perception are due to differences in concurrent levels of circulating gonadal hormones (*19*). Similar sex differences have been noted in vision, audition, touch, and kinesthesis (*20*).

As in most sensory systems, the anatomic and physiologic bases for the age-related changes in smell ability are probably multiple, interacting, and complex. Although the causes of the changes are not known, there is strong circumstantial evidence that degenerative processes within the olfactory epithelium may be involved. Histological studies of human and rodent olfactory epithelia and olfactory bulbs reveal striking differences between old and young specimens (*21*), and viruses and chronic inflammatory nasal diseases are known to adversely affect olfactory receptors (*22*). Anosmia due to upper respiratory infection of viral origin occurs more often in clinic patients over the age of 50, suggesting that the olfactory epithelium of older individuals may be less resistant to viral attack (*23*).

In addition to damage to the olfactory receptor epithelium, changes in more central neural pathways may also contribute to age-related decreases in olfactory function. Such a hypothesis gains support from studies demonstrating relations between aging and behavioral events correlated with the activity of specific neurotransmitters (for example, arousal, attention, and memory) (*24*), and recent evidence that scores on the smell identification test used in this study are significantly correlated, in Korsakoff's psychosis patients, with cerebral spinal fluid levels of a major metabolite of norepinephrine (*7*).

Regardless of the neuroanatomical bases of these changes, the data strongly suggest that large numbers of elderly persons have major dysfunction of the olfactory sense. Indeed, these data reveal that (i) more than 80 percent of the persons tested over the age of 80 years evidenced major olfactory impairment, with nearly 50 percent being anosmic, and (ii) more than 60 percent of the persons tested aged between 65 and 80 years evidenced major olfactory impairment, with nearly a quarter being anosmic (*25*). Given these findings, it is not surprising that many elderly persons complain that their food lacks flavor (*26*). Aside from influencing food intake and nutrition (*27*), decreased smell function undoubtedly compromises the ability of this expanding segment of society to detect and avoid life-threatening fires and gas leaks in the home (*28*).

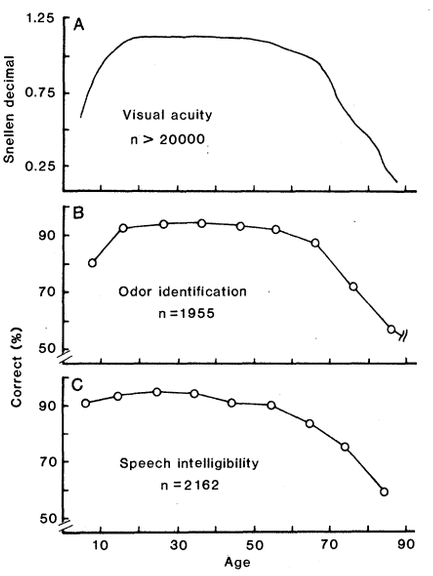

Fig. 2. Suprathreshold measures across age for three major sensory systems. Data on visual acuity are from figure 8 in (*14*); data on speech intelligibility (PB_{max}) are modified from figure 2 in (*13*).

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Evidence for Cholinergic Neurites in Senile Plaques

Abstract. *In the neocortices and amygdalae of young and aged macaques, cholinergic axons were identified by means of a monoclonal antibody to bovine choline acetyltransferase. Many fine, linear, immunoreactive profiles were seen in these animals. In the older animals, some cholinergic axons showed multifocal enlargements along their course. In some instances, neurites with choline acetyltransferase immunoreactivity were associated with deposits of amyloid (visualized with thioflavin T fluorescence). The appearance of these amyloid-associated abnormal cholinergic processes was similar to that of neurites in senile plaques, as shown by conventional silver impregnation techniques. Cholinergic systems thus give rise to some of the neurites within senile plaques.*

Senile plaques, consisting of enlarged axons or nerve terminals (neurites) close to amyloid cores, are present in the amygdala, hippocampus, and neocortex in aged humans (*1*), in aged nonhuman primates (*2, 3*), and, in exaggerated numbers, in individuals with Alzheimer's disease and its late-life variant, senile dementia of the Alzheimer's type (*4*). In Alzheimer's disease there are alterations in markers for several neurotransmitters, including cholinergic, monoaminergic, and somatostatinergic systems; cortical cholinergic markers [such as choline acetyltransferase (ChAT), acetylcholinesterase (AChE), uptake of ^{3}H-labeled choline, and synthesis of acetylcholine from isotopically labeled glucose] show the earliest, most consistent, and most severe decrements (*5*). Reductions in neocortical cholinergic markers correlate with the presence of senile plaques (*6*) and appear to result from dysfunction and death of neurons located within the basal forebrain cholinergic system (*7*), which innervates cortical regions (*8*).

Because these cholinergic neurons of the medial septum, diagonal band of Broca, and nucleus basalis of Meynert are rich in AChE (*9*) and because abnormal intracortical neurites in plaques of aged primates contain AChE (*3, 10, 11*), we postulated that some of the axonal swellings in senile plaques may be derived from the basal forebrain cholinergic system (*3, 12*). However, AChE is not a specific marker for cholinergic systems in that it is present in neurons in various subcortical nuclei that project to the cortex (for example, noradrenergic nerve cells of the locus coeruleus, dopaminergic neurons of the substantia nigra and ventral tegmental area, and serotonergic neurons of the nucleus raphe); at least in culture, AChE is also present in cortical neurons containing γ-aminobutyric acid or somatostatin (*13, 14*). Therefore, axons derived from these noncholinergic neuronal populations and perhaps from other cell groups that do not stain by AChE histochemical techniques may also contribute to neurites in senile plaques.

To test directly the hypothesis that senile plaques contain cholinergic elements, it is necessary to show that ChAT, a specific marker for cholinergic neurons (*15*), is present in the neurites of plaques. By means of a monoclonal antibody to ChAT and immunocytochemical techniques, we now show that cholinergic neurites are present in the neocortices and amygdalae of aged macaques and directly link the cholinergic system to the senile plaque, a major histopathological hallmark of Alzheimer's disease.

Two healthy young (~5 years of age) macaques (*Macaca mulatta*) and five aged macaques (males and females from approximately 20 to 30 years of age) were anesthetized and perfused with fixatives (*16*); tissues were prepared (*17*) for morphological—including immunocytochemical (*18*) and histochemical (*19*)—studies.

Sevier-Munger silver stains of the neocortices and amygdalae of the older monkeys revealed scattered senile plaques consisting of irregular, knob-shaped neurites and deposits of amyloid (Fig.