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11. An item analysis revealed that a statistically significant decrease in performance occurred for each odorant across the age range. Although the percentage of correct identification differed slightly among the stimuli across age, these differences are difficult to interpret given the diversity of suprathreshold psychophysical response functions among odorants [R. L. Doty, *Percept. Psychophys.* **17**, 492 (1975)] and the multichemical basis of some of the stimuli.
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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.

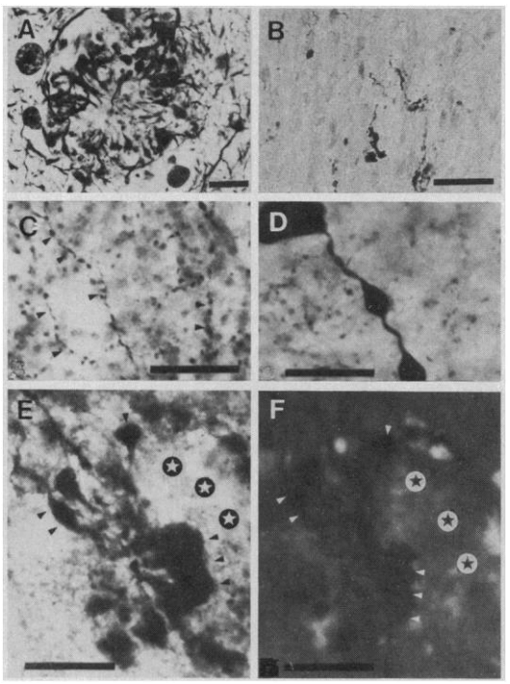

Fig. 1. (A) A neurite-rich senile plaque, shown by silver-impregnation techniques, in the neocortex of a 21-year-old monkey. Arrows indicate neurites. Scale, 20 μm. (B) Swollen fibers with ChAT immunoreactivity in the neocortex of a 21-year-old monkey. Scale, 50 μm. (C) Normal processes with ChAT immunoreactivity in the amygdala of a young macaque. Arrows indicate several fibers. Scale, 20 μm. (D) Swollen fibers with ChAT immunoreactivity in the neocortex of a 21-year-old monkey. Scale, 20 μm. (E) This combined immunocytochemical and thioflavin T–stained (amyloid) preparation shows a cluster of neurites with ChAT immunoreactivity (arrows) adjacent to a deposition of amyloid (asterisks). Scale, 20 μm. (F) The same microscopic field as in (E) stained with thioflavin T and examined under fluorescence microscopy, showing the proximity of amyloid (asterisks) to the elements with ChAT immunoreactivity (arrows). Scale, 20 μm.

1A). Plaques were not seen in these regions in young monkeys.

Immunocytochemical studies of the neocortices and amygdalae of young animals disclosed thin processes with ChAT immunoreactivity that rarely contained small varicosities. Punctate deposits of reaction product in the neuropil were interpreted as representing synaptic terminals. No amyloid was seen in the younger animals. In older macaques, the neocortex contained many fibers with ChAT immunoreactivity that were identical to those seen in young animals (Fig. 1C). In addition, in the cortex of older animals there were abnormal immunoreactive axons with multiple, irregular swellings along their course (Fig. 1, B and D). These abnormal fibers were most conspicuous in the medial orbital cortex and precentral gyrus and within the cingulate cortex. Some immunoreactive processes formed spray-like arrays. The results of combined ChAT immunohistochemistry and thioflavin T staining (amyloid) showed that some clusters of neurites with ChAT immunoreactivity were associated with deposits of amyloid (Fig. 1, E and F) but also showed some deposits of amyloid not associated with demonstrable cholinergic neurites. Most of the abnormal cholinergic axons and neurites, visualized with our immunocytochemical protocols for ChAT, were similar to structures elucidated by means of a modified histochemical method for AChE (*10*) in the neocortices of old monkeys. Images obtained with AChE histochemistry and ChAT immunocytochemistry resembled the silver-impregnated neurites seen in senile plaques of aged primates (Fig. 1A), indicating that cholinergic elements are present in some senile plaques.

Our results are apparently the first direct evidence that some of the neurites in plaques are cholinergic. The source of these neurites is probably cholinergic neurons in the basal forebrain; therefore, forebrain cholinergic systems appear to be directly related to a major histopathological change in the brains of aged humans and patients with Alzheimer's disease. Similar immunocytochemical approaches can be used to examine the possible roles of other transmitter-specific systems in senile plaques in aged primates. Other studies from our laboratory have indicated that monoaminergic and peptidergic systems also contribute to plaques in aged primates (*20*). It is not known whether all the neurites in an individual plaque are of one transmitter type (homogeneous plaque) or are derived from several neuronal systems having different neurotransmitter specificities (heterogeneous plaque) (*12*). This issue can be addressed by immunocytochemical colocalization studies and by examining the relation of neurites to amyloid in immunocytochemically stained serial sections with the use of a number of different antibodies. The aged nonhuman primate provides a model useful for studying the sources and transmitter specificities of some of the pathological processes in the central nervous system of normal aged individuals.

Senile plaques are a common neuropathological finding in the amygdala, hippocampus, and neocortex in senile dementia of the Alzheimer's type, and the number of senile plaques correlates with the presence of cognitive impairment in these individuals (*4*). Although there is evidence for abnormalities of cholinergic and noncholinergic systems in Alzheimer's disease (*5, 7, 21*), the transmitter specificities of neurites in senile plaques have not been systematically analyzed in the human brain. The approach described above should be useful in delineating the abnormalities in transmitter-specific systems in the brains of individuals affected with Alzheimer's disease and related disorders.

Note added in proof: Although we have not yet been successful in demonstrating ChAT-immunoreactive neurites in plaques in humans, we have shown, by immunocytochemical techniques, axonal abnormalities of peptidergic systems in the brains of aged humans.

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16. Subjects were restrained with ketamine (5 to 10 mg per kilogram of body weight), anesthetized with sodium pentobarbital (32.5 mg per kilogram) administered intravenously, heparinized (400 units per kilogram), and given 2 ml of 1 percent sodium nitrite intravenously. The animals were perfused with 4 liters of cold saline solution (0.9 percent) prepared in 0.1*M* phosphate buffer (*p*H 7.4) and then with 12 liters of cold paraformaldehyde (4 percent) and glutaraldehyde (0.1 to 0.2 percent) in 0.1*M* phosphate buffer (*p*H 7.4). A 26-year-old macaque was restrained with ketamine and suffered a cardiac arrest. After cardiopulmonary resuscitation, the animal was heparinized and perfused via the left ventricle with 4 liters of cold saline (0.9 percent) for 5 to 10 minutes, then with 10 liters of acetate-buffered Formalin (10 percent, *p*H 6.5) for 30 minutes, and finally with 7 liters of acetate-buffered Formalin and glutaraldehyde (10 and 0.16 percent, respectively) for 15 minutes.
17. After perfusion, the brains were blocked into coronal slabs (2 to 5 mm). Some tissue sections were cut (50 to 100 μm) on a Vibratome (Lancer) and collected in cold 0.1*M* tris-buffered saline (TBS, *p*H 7.6); remaining tissues from these monkeys were stored in 30 percent sucrose in 0.1*M* phosphate buffer (*p*H 7.4) overnight, frozen on dry ice the next day, cut at 40 μm on a sliding freezing microtome (American Optical), and collected into cold TBS.
18. For immunocytochemistry, sections were incubated and treated with solutions as follows. (i) Triton X-100 (0.4 percent, Sigma) in 0.1*M* TBS (*p*H 7.6) for 20 minutes (20°C); (ii) normal goat serum (3 percent, Dako) in Triton X-100 (0.1 percent) and 0.1*M* TBS for 30 to 60 minutes (20°C); (iii) antibody to ChAT (1:500 to 1:2000) (*14*) in the same solution containing 1 percent normal goat serum for 24 to 48 hours (4°C) with three subsequent rinses (5 minutes each) in cold TBS; (iv) goat antibody to mouse immunoglobulin (1:100, Cappell) in Triton X-100 (0.1 percent) and 0.1*M* TBS containing normal goat serum (1 percent) for 1 hour (4°C) with three subsequent rinses (5 minutes each) in cold TBS; (v) a complex of mouse peroxidase and monoclonal antibody to peroxidase (peroxidase-antiperoxidase; 1:100, Sternberger and Meyer) in 0.1*M* TBS containing normal goat serum (1 percent) for 1 hour (4°C) with three subsequent rinses (5 minutes each) in cold TBS; (vi) a fresh solution of goat antibody to mouse immunoglobulin (1:100) without Triton X-100 for 1 hour (4°C) and three subsequent rinses (5 minutes each) in cold TBS; (vii) a fresh solution of mouse peroxidase-antiperoxidase (1:100) for 1 hour (4°C) with three subsequent rinses (5 minutes each) in cold TBS; (viii) 3,3′-diaminobenzidine tetrahydrochloride (0.05 percent, Aldrich) and H_2O_2 (0.01 percent, Mallinckrodt) in 0.1*M* TBS for 5 to 15 minutes (20°C); (ix) as a control, rat immunoglobulin (1:500 to 1:2000, Sigma) from a stock solution (1 mg of protein per 1 ml of TBS) replaced the antibody to ChAT. Sections were washed in TBS and mounted out of acetate buffer (*p*H 6.0) onto slides that had been coated with chrome-alum. All sections were dehydrated through alcohols and xylenes and mounted with glass cover slips and Permount. Selected sections were treated with OsO_4 (0.05 percent) in H_2O for 0.5 to 1.0 minute and mounted. Finally, selected sections were counterstained with cresyl violet to visualize nuclear groupings.
19. Some slides were stained with thioflavin T (Roboz) as described [P.S. Vassar and C. F. A. Culling, *Arch. Pathol.* **68**, 487 (1959)].
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Common Region on Chromosome 14 in T-Cell Leukemia and Lymphoma

Abstract. *Chromosome 14 breakpoints in malignant human lymphocytes cluster on the long (q) arm near bands q11 and q32. An inversion of chromosome 14 due to breaks in q11.2 and q32.3 has now been found in a newly established childhood T-cell lymphoma cell line and confirmed in T-cell chronic lymphocytic leukemia. A translocation was also found between chromosomes 10 and 14 with a breakpoint at 14q11.2 in another T-cell lymphoma cell line. It is proposed that a proximal region on chromosome 14 in or near sub-band q11.2 is related to T-cell function. Rearrangements in this region may affect the growth of T lymphocytes and be involved in the development of T-cell malignancies.*

Nonrandom chromosome abnormalities mark certain forms of human cancer (*1*). In T-cell chronic lymphocytic leukemia (CLL), an inversion of chromosome 14 due to a break proximally in band q11 and a break distally in band q32 has been reported (*2, 3*). We have observed this chromosome 14 inversion in an established T-cell lymphoma cell line and confirm its occurrence in T-cell CLL. However, the change in chromosome 14 in T-cell malignancies can also be a translocation. The common feature appears to be rearrangement of the proximal region on 14q.

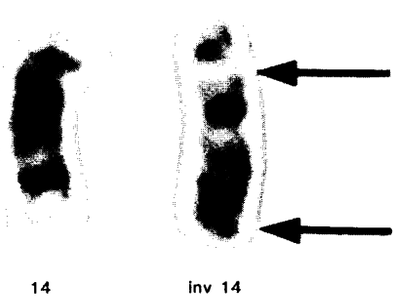

Fig. 1. High-resolution G banding of normal chromosome 14 (left) and inverted chromosome 14 (right) with arrows pointing to breakpoints in q11.2 (above) and q32.3 (below) in T-cell lymphoma cell line SUP-T1.

A T-cell lymphoma cell line (SUP-T1) (*4*) was established from a pleural effusion in a 6-year-old boy who was diagnosed 15 months earlier as having lymphoblastic lymphoma. There was no involvement of bone marrow or central nervous system. The pleural effusion cells, which appeared uniformly malignant, were cultured (*5*). These cells were E-rosette negative at 4° and 37°C and negative for monoclonal antibodies to Leu 5, OKT9, CALLA (common acute lymphocytic leukemia antigen), Ia (I region–associated antigens), and SIg (surface immunoglobulin) but were positive for antibodies to Leu 1, 2a, 3a, 4, 6, and 9 and OKT10. This antigen profile is consistent with T-cells of mid-thymocyte type. Chromosome preparations were made for high-resolution G banding. The karyotype was 46,XY with an inversion of chromosome 14: inv(14)(q11.2q32.3) (Figs. 1 and 2).

The patient with T-cell CLL was a 59-