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Clinico-pathologic studies in dementia:
Nondemented subjects with pathologically confirmed Alzheimer's disease

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Article abstract—We compared neuropsychological findings in 28 longitudinally evaluated elderly subjects with their postmortem neuropathology, including senile plaque and neurofibrillary tangle counts from standardized sections. Nine of the subjects were not demented when evaluated just prior to their death. Numerous cortical senile plaques and other changes of Alzheimer's disease (AD) occurred in six of nine nondemented old-old subjects. Five of these six subjects had shown decline on yearly neuropsychological tests but their cognitive impairment was too mild to meet clinical criteria for dementia. Whereas cortical senile plaque count did not distinguish well between demented and nondemented subjects, every subject with numerous cortical neurofibrillary tangles was demented. The nondemented subjects with Alzheimer pathology may have had "preclinical" AD, or numerous cortical plaques may occur in some elderly subjects who would never develop clinical dementia.

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The pathologic criteria for the diagnosis of AD are age-dependent[1] and reflect the fact that cortical senile plaques are rare in nondemented subjects in their 60s, but occur in 75 to 80% of nondemented subjects in their 80s.[2] Nondemented subjects in their 80s usually have fewer cortical senile plaques than demented subjects of the same age.[2] We now report on clinicopathologic findings in 28 subjects who had been followed longitudinally with yearly neuropsychological evaluations. Numerous cortical senile plaques were common in most subjects, including six who were not clinically demented. Preliminary reports of these data have appeared elsewhere.[3-5]

Methods. *Subjects.* Eleven subjects were from the Bronx Aging Study and 17 patients were from the Albert Einstein Teaching Nursing Home Study. The Bronx Aging Study was designed to identify the very earliest signs of dementia and to define cognitive characteristics of an old-old population. Criteria for inclusion in the Bronx Aging Study were (1) age 75 to 85 years of age; (2) absence of dementia as shown by a score of

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Table 1. Age and sex of study subjects

Clinical Dx	N	Age (mean)	M/F
Normal	4	86	1/3
CC	5	87	1/4
AD	13	78	6/7
MID	3	81	0/3
DU	3	75	2/1

N Number of subjects.
CC Cognitive change.
AD Alzheimer's disease.
MID Multi-infarct dementia.
DU Dementia unspecified.

8 or less on an Americanized form of the Blessed test of orientation, memory, and concentration (Blessed OMC test)[6-8] and lack of social or occupational decline[9]; and (3) medically able to participate in a long-term longitudinal study. The Teaching Nursing Home Study was designed to measure longitudinal cognitive and neurologic changes in demented subjects. Subjects in the Teaching Nursing Home Study could not be suffering from a terminal illness and must have had no history of major psychiatric illness.

Clinical evaluation. Subjects from both studies were evaluated with yearly neuropsychological and neurologic evaluations. All demented subjects were evaluated with CT, EEG, and appropriate blood studies. Diagnoses of dementia, probable Alzheimer's disease (AD), possible AD, and multi-infarct dementia were made according to established criteria.[9-11] When neurologists on the study team agreed that a subject was demented, but could not agree on the type of dementia, a diagnosis of "dementia—type unspecified" was made.

Testable subjects were evaluated yearly on the Blessed OMC test,[7,8] on trial one of the Fuld Object Memory Evaluation,[12] and usually on the Wechsler Adult Intelligence Scale (WAIS).[13] Level of function was also assessed by completing an activities-of-daily-living questionnaire on demented subjects.[7]

Fifteen of the 28 subjects were examined within 6 months of death, and 25 of the 28 within 12 months of death. Three subjects were examined 19 to 28 months before death. We assessed neuropsychological status prior to time of death in these subjects by reviewing their medical records and by interviewing family members.

We used the term "cognitive change" to describe subjects who did not meet criteria for dementia but who showed a consistent decline on neuropsychological test scores.

Pathology. Senile plaques were counted by means of thioflavine S staining and fluorescent microscopy at 100× power in a field measuring 1.41 mm^2, and then normalized to a 1 mm^2 area. We counted three contiguous fields from the midfrontal gyrus (Brodmann area 9) that had been cut perpendicularly to the cortical surface. When more than 50 plaques were present, the plaque count was recorded as 50. In cases with very many plaques, it was often difficult to arrive at a more precise number. Neurofibrillary tangles were counted at 400× power in a field measuring 0.37 mm^2. Pathologic evaluation also included routine sections from five neocortical areas, in addition to hippocampus, amygdala, basal forebrain, basal ganglia, midbrain, pons, medulla, and cerebellum. Additional staining methods were employed on all sections to confirm the findings with thioflavine S fluorescent microscopy, including Bodian and Bielschowsky silver impregnation methods to stain neuritic elements and alcian blue and Congo red to stain amyloid. We noted the number and size and estimated the volume of the ischemic lesions. Presence or absence of cell loss in the basal nucleus of Meynert, the substantia nigra, and locus ceruleus was noted in all cases. We examined the basal ganglia and cerebellar sections for degenerative changes.

We noted both plaque morphology and number. With thioflavine S it is possible to recognize plaques ranging from 5 to 200 microns in diameter. These plaques have variably pale or granuloreticular fluorescence but lack a well-defined compact amyloid core, and have been referred to as "primitive plaques." Senile plaques with cores are referred to as "classic plaques."

We defined "mixed dementias" by the presence of pathologic changes of AD together with multiple lacunes, or at least 50 cm^3 of tissue loss from a cerebral infarction. Subjects with only one or two lacunes and AD were classified pathologically as AD (with concomitant infarcts).

Statistics. Pearson's product moment correlation coefficients were used to relate plaque count and neuropsychological scores.

Results. Four patients were cognitively normal, five showed cognitive change but not dementia, and 19 were demented. Table 1 lists demographic characteristics of these subjects. One cognitively normal subject and one subject with cognitive change had lived in a nursing home for several years because of visual or orthopedic handicaps. The remaining seven nondemented subjects lived at home and were independent in all activities of daily living until just prior to death. All nine nondemented subjects had been retired for several years; thus cognitive deficits sufficient to have impaired their ability to work could not be detected.

Serial neuropsychological scores from the four normal subjects and the five subjects with cognitive change are listed in table 2. The normal subjects showed fluctuations, but no consistent decline in test scores. The subjects with cognitive change showed decline on at least one and most often several tests. Four of five subjects with cognitive change had marked decline on the Fuld Object Memory Evaluation.

The 19 demented subjects all required substantial help with feeding, dressing, and personal hygiene because of their cognitive impairments. Thirteen had a clinical diagnosis of AD, three a clinical diagnosis of multi-infarct dementia, and three a diagnosis of "dementia—type unspecified."

Figure 1A illustrates the total plaque counts in the frontal cortex in our subjects. Three of four normal subjects had fewer than 15 SP/mm^2 in the frontal cortex. All five subjects with cognitive change had more than 30 SP/mm^2 in the frontal cortex. Of 13 patients with clinical diagnosis of AD, 11 had numerous frontal plaques and met other criteria for the pathologic diagnosis of AD. Thus the clinical diagnosis of AD was confirmed at postmortem in 85% of cases. All three subjects with MID also had multiple cortical plaques but no cortical tangles. Cortical plaques were absent in two of the three patients in whom the type of dementia was uncertain.

Figure 1B summarizes neurofibrillary tangle counts in the frontal cortex in the subjects. No frontal tangles were found in normal subjects, and no more than 3 NFT/mm^2 were found in subjects with cognitive change. One-half of the demented subjects had no

Table 2. Serial neuropsychological test scores in nondemented subjects

Pt	DOE	Blessed OMC	FOME‡	VIQ	PIQ
Normal					
6	11/81	0	9	112	107
	3/82	1	9	106	96
	12/82	2	6	—	—
	10/83	0	9	107	96
7	6/84	0	—	106	96
	2/85	—	—	114	—
8	9/81	2	7	—	—
	3/83	5	8	110	120
	6/84	5	10	110	110
	8/85	4	—	—	—
9	6/81	—	9	—	—
	12/82	0	8	—	—
	10/83	1	7	—	—
	7/86	0	9	—	—
Cognitive change					
10	11/80	2	9	134	117
	3/82	4	6	—	—
11	4/81	6	4	98	102
	4/83	7	6	99	90
	8/84	8	4	98	84
12	5/81	2	—	—	—
	10/81	—	—	115	104
	4/83	2	7	104	100
	8/83	3	5	—	—
13	1/81	2	8	119	104
	2/82	2	8	119	104
	6/83	2	7	124	98
	10/84	1	6	119	96
	8/85	3	4	104	87
14	8/83	1	—	—	—†
	12/83	—	4	—	—†
	11/84	6	—	—	—†
	1/85	7	—	—	—†
	7/86	7	2	134	—†
	9/86	27*	—	—	—†

* Subject's last evaluation 1 month prior to death showed lethargy and decreased attention. The marked cognitive deterioration prior to death was probably related to a metabolic encephalopathy associated with her terminal illness. For this reason the subject was classified as having cognitive change despite her poor final Blessed score.
† Patient was blind and performance IQ test could not be administered.
‡ Mean score of 477 nondemented subjects, 75-85 years old, on Recall I of the FOME is 7.28 ± 1.32 (D Masur, unpublished data).
— Data not available.
DOE Date of examination.
Blessed OMC Blessed test of orientation, memory, and concentration.
FOME Fuld Object Memory Evaluation.
VIQ Verbal IQ from the Wechsler Adult Intelligence Scale (WAIS).
PIQ Performance IQ from the WAIS.

frontal tangles, including three subjects with clinical diagnosis of MID, two with dementia unspecified, and four with clinical diagnosis of AD. The remaining nine demented subjects had between 3 and 35 NFT/mm^2.

Nine subjects with pathologic diagnoses of AD were over 75, and thus did not require cortical tangles for pathologic diagnosis. Nonetheless, cortical tangles were found in six of these subjects.

Figure 1, C and D, illustrate plaque and tangle counts in the hippocampus. Subjects with very high plaque or tangle counts in the hippocampus were usually demented. Thus 8/9 subjects with more than 21 SP/mm^2 in the hippocampus were demented. Similarly, 7/8 subjects with more than 50 NFT/mm^2 in the hippocampus were demented.

The relative percentage of "plaques with cores" and more primitive plaques did not differ between the demented and nondemented subjects. Most subjects with AD had the same number of plaques with cores in the frontal cortex as nondemented subjects (figure 2).

The association between the count of plaques without cores (primitive plaque count) in the frontal cortex and score on the Fuld Object Memory Evaluation is illustrated in figure 3 ($R = 0.65$, $N = 11$, $p < 0.03$). Over half of the data points cluster around high plaque counts with borderline or impaired memory test scores. Whereas the correlation between Fuld Object Memory score and primitive plaque count was strong, there was a poor correlation between the Fuld score and number of plaques with cores ($R = -0.13$, $N = 11$).

Figure 4 shows the association between total plaque count in the frontal cortex and the Blessed OMC score ($R = 0.57$, $N = 18$, $p < 0.01$). Scores were not evenly distributed; there was a large cluster of very demented subjects with high plaque counts, and a smaller cluster of nondemented subjects with low plaque counts.

Table 3 lists the clinical and pathologic characteristics of the five demented subjects with non-Alzheimer dementias. Subject 2 was diagnosed as having AD, although one neurologist felt that his preserved ability to copy line drawings was atypical. This non-Guamanian subject had ALS-dementia. When he was last examined, 2 years prior to his death, dementia was severe and motor findings were absent. Subject 3 had a history of alcohol intake averaging 4 to 5 shots per day for about 10 years until the time of onset of his cognitive impairment. He abstained from alcohol thereafter, but his cognitive impairment progressed. Neuropsychological testing showed that he was quite good at the digit-symbol test from the WAIS, a test that usually is very difficult for AD patients. One neurologist made a clinical diagnosis of AD, a second diagnosed alcoholic dementia. Postmortem showed hippocampal ischemia and rare cortical neurofibrillary tangles, but no tangles in the hippocampus and no senile plaques. The initial diagnosis in subject 5 was hydrocephalus because gait disorder and incontinence preceded marked memory impairment, and central atrophy predominated on CT. However, as she became more demented, her clinical diagnosis was changed to AD. Postmortem showed multiple infarcts, white matter degeneration suggestive of Binswanger's disease, and numerous cortical plaques but no tangles. No plaques or tangles were present in the hippocampus. Subjects 1 and 4 met clinical criteria for probable AD, and thus had no atypical features.

Cerebral infarcts were found on examination of the

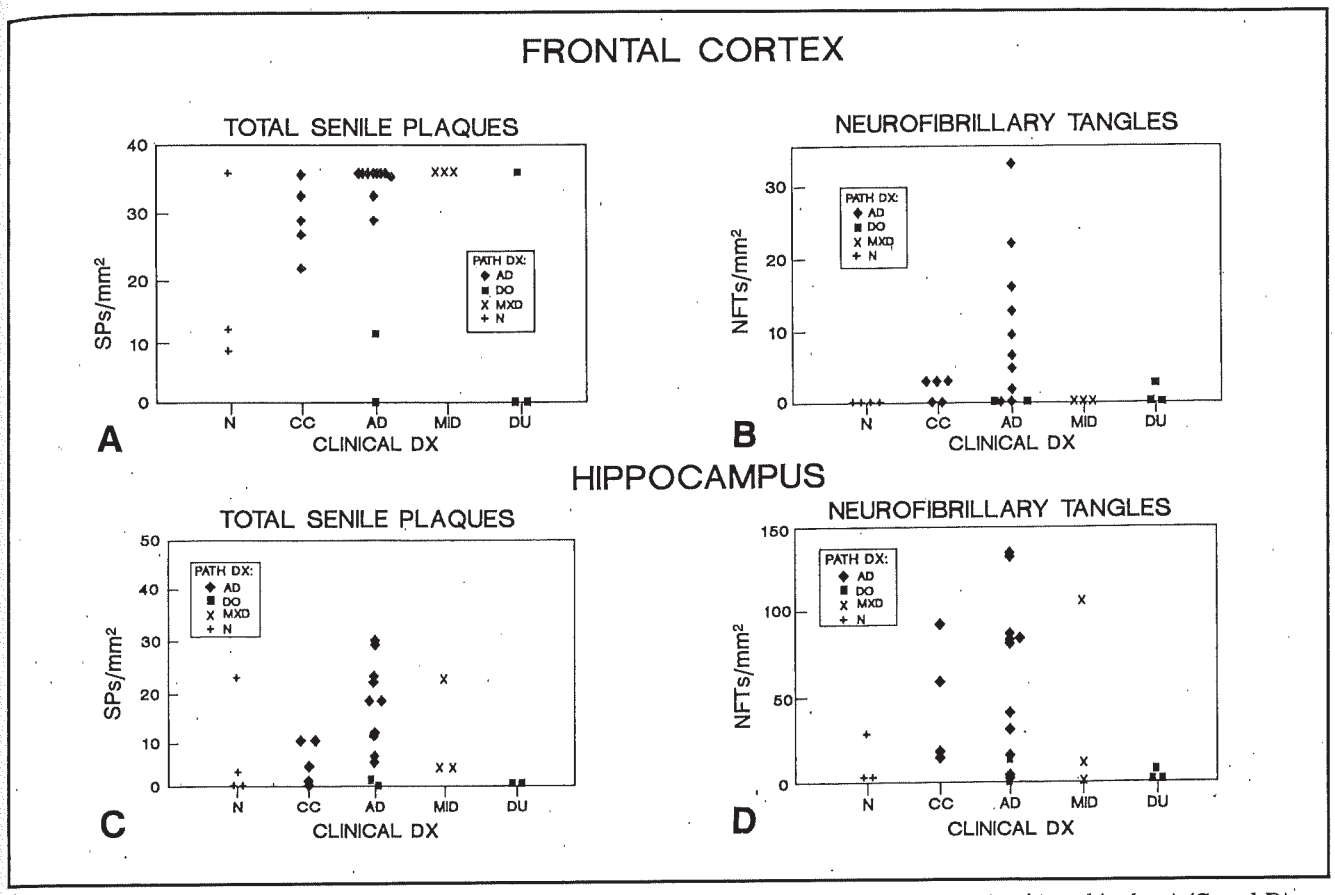

Figure 1. Total plaque and tangle count in frontal cortex (A and B) and in the hippocampus (ca1 + subiculum) (C and D). Subjects are grouped on the x-axis according to clinical diagnosis; different symbols denote different pathologic diagnoses. N = normal; AD = Alzheimer's disease; CC = cognitive change; MID = multi-infarct dementia; DO = dementia other than Alzheimer's, multi-infarct, or mixed; DU = dementia, type unspecified; MXD = mixed dementia. Clinical and pathologic diagnoses followed criteria defined in text.

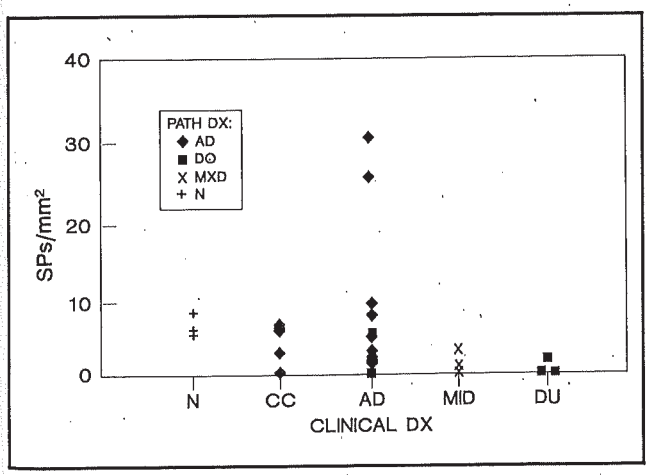

Figure 2. Senile plaques with cores in the frontal cortex.

right cerebral hemisphere, brainstem, and cerebellum in ten of the 28 subjects (the left cerebral hemisphere was used for neurochemical studies). Table 4 summarizes the site of infarcts in these subjects. In every case where subjects were suspected clinically of having had a cerebral infarct, an infarct was found on postmortem. In contrast, infarcts were found on postmortem in six subjects when these lesions were not suspected clinically. In three of these cases, the unsuspected lesions were one or two lacunes. Infarcts occurred in 2/9 nondemented subjects, and 8/19 demented subjects.

Adequate midbrain specimens were available for ten of the AD subjects. Five of these subjects had occasional Lewy bodies and a mild to moderate amount of cell loss in the substantia nigra. Two of the subjects with substantia nigra pathology also had occasional cortical Lewy bodies. One subject had both many senile plaques and cortical Lewy bodies but no tangles when she died at age 71. An unusual feature of her illness was coexistent hyperactive, agitated behavior and parkinsonian resting tremor. The other subject had classic pathologic changes of AD in addition to cortical Lewy bodies. Her clinical course was consistent with probable AD.

Fourteen of 16 subjects who met pathologic criteria for AD or mixed dementia had at least some cell loss in the nucleus basalis. The two subjects who had no cell loss in the nucleus basalis had numerous frontal plaques but no frontal tangles, and also had few hippocampal plaques. One of these subjects had a clinical diagnosis of cognitive change, the other had a clinical diagnosis of multi-infarct dementia. Every subject with moderate or severe cell loss in the nucleus basalis was clinically

Table 3. Demented subjects who did not meet pathologic criteria for Alzheimer's disease

Clinical Dx	Pathologic Dx	Age onset	Comments
AD	Lobar atrophy without Pick bodies	62	Course met criteria for probable AD
DU	ALS-dementia	48	American-born; motor signs absent at least until moderate dementia; copied line drawings very well
DU	Hippocampal sclerosis, thalamic degeneration	71	Able to learn novel tasks such as block design; had progressive course
AD	Parkinson's disease vs Lewy body disease	78	Motor signs absent except for mild shuffling gait
DU	Multiple infarcts and Binswanger's leukoencephalopathy	87	Gait problems and incontinence antedated cognitive decline by 1-2 years

DU Dementia, type unspecified.

Table 4. Cerebral infarcts found on microscopic examination of the left cerebral hemisphere, brainstem, and cerebellum

Cognitive status	Infarcts clinically suspected (Y/N)	Type/site and size of infarct
Demented (N = 8)	Y	Anterior temporal and frontal (>100 cm^3)
	Y	Multiple lacunes; basal ganglia, occipital, pons
	Y	Lacunes in basal ganglia, thalamus, large anterior temporal (acute)
	N	3-4 cm^3 bland, frontoparietal
	N	Lacune in pons
	N	Two lacunes; caudate and inferior temporal
	N	"Ischemic injury" Ammon's horn
	N	Lacunes in thalamus, midbrain, pons, and subacute in occipital
Not demented (N = 2)	Y	<5 cm^3 globus pallidus and adjacent internal capsule
	N	Two lacunes; frontal lobe and pons

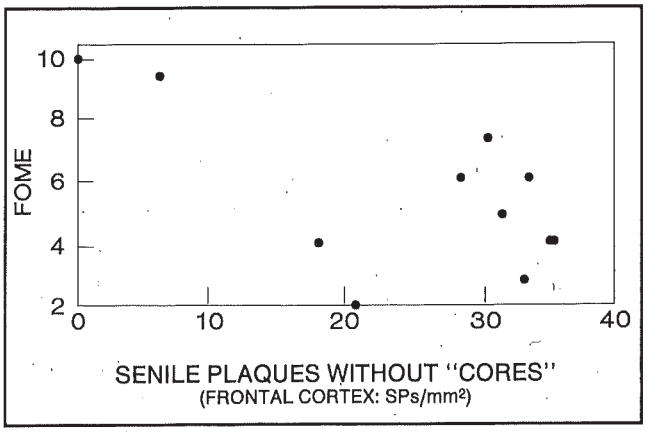

Figure 3. The association of the count of plaques without cores in the frontal cortex with score on recall I on the Fuld Object Memory Evaluation.

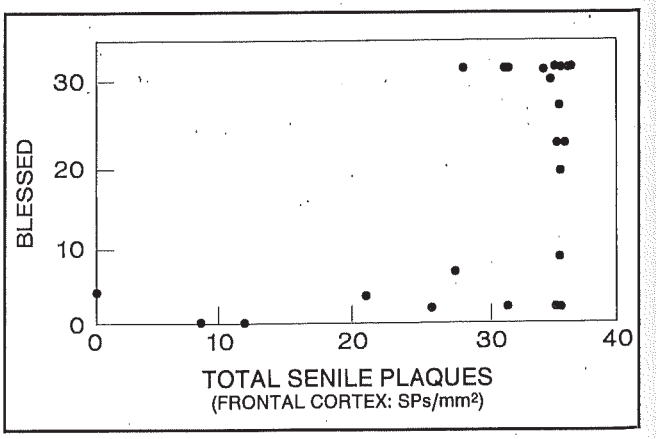

Figure 4. The association of total plaque count in the frontal cortex and score on the Blessed OMC.

demented and also met pathologic criteria for AD. About one-third of subjects with pathologic diagnoses of AD had no cell loss in the substantia nigra or in the locus ceruleus.

Senile plaque counts in the cerebellum were available for 24 subjects. Numerous cerebellar senile plaques occurred in seven subjects. All seven were clinically demented and had widespread pathologic evidence of AD.

Discussion. This study compares neuropsychological findings in prospectively evaluated elderly patients with postmortem neuropathology, including standardized plaque and tangle counts in sections of neocortex and hippocampus. Our major finding is that there are numerous senile plaques in the frontal cortex in elderly subjects who show cognitive change but not dementia. One of four cognitively normal subjects, and all five subjects with cognitive change but not clinical dementia, had numerous frontal plaques and met other pathologic criteria for AD.

Eighteen subjects were over 80 at time of death. Greater than 30 SP/mm^2 in the frontal cortex occurred

in 14 of these subjects including 6/9 nondemented subjects. Whereas two-thirds of our nondemented subjects had numerous neocortical senile plaques, Katzman et al[14] reported that only one-third of their elderly nondemented subjects had numerous plaques. Because of the high sensitivity of thioflavine in detecting senile plaques, data from this study may not be comparable to studies where senile plaque counts were determined with silver stains. The majority of plaques in most demented and nondemented subjects were of the primitive or very primitive type without cores, precisely the type of plaques most poorly detected with some silver stains.

The central question our study raises is whether the subjects meeting pathologic criteria for AD were in a stage of early AD and would have become clinically demented had they lived longer, or whether the pathologic criteria for AD in very old subjects need to be revised. More sensitive neuropsychological criteria may be needed to identify the earliest stages of AD. In very old subjects, many of whom live in nursing homes or other protected environments, the criteria for social or occupational decline[9] are harder to meet than in younger subjects who are still working. If criteria for dementia included social decline or significant decline from baseline on traditional neuropsychological tests, at least two other subjects would have been considered demented since they showed 16% and 18% decline in performance IQ. Four of six subjects with cognitive decline showed marked deterioration on the Fuld Object Memory Evaluation. If significant decline on this test were used as an indicator of clinical dementia, concordance of clinical and pathologic diagnoses would have improved substantially.

Another way to improve the concordance between clinical and pathologic diagnoses would be to change the pathologic criteria for diagnosing AD. If both plaques and tangles in the frontal cortex were required to meet pathologic criteria for AD regardless of age, then only two of the five subjects with cognitive change, and none of the cognitively normal subjects would have met criteria for AD. Our data indicate that more than three cortical NFTs/mm^2 was always associated with dementia. The three nondemented subjects who averaged three cortical NFTs/mm^2 showed the most severe cognitive changes (subjects 11, 13, and 14) of all nine nondemented subjects. Cortical neurofibrillary tangles were not found in any of the other six nondemented subjects.

On the other hand, seven demented subjects had numerous senile plaques but no cortical tangles. Five of these seven subjects had pathologic processes other than senile plaques, which could account at least in part for their dementia; this includes four subjects with multiple infarcts and one subject with cortical Lewy bodies. Whereas the association between cortical neurofibrillary tangles and dementia is compelling, the association between cortical senile plaques and dementia is less clear.

Our data suggest a correlation between primitive plaque count and memory as measured on the Fuld Object Memory Evaluation. How can we argue that numerous primitive cortical plaques are associated with memory impairment and at the same time argue that numerous plaques do not distinguish between demented and nondemented subjects? We were able to analyze the correlation between memory score and plaque count for only 11 of our subjects because we insisted that the test have been administered within 12 months of the patient's death. This memory test is too difficult for patients with moderate dementia. Accordingly, although several subjects showed impaired memory, only two of the 11 subjects were demented when they took the test. Numerous primitive senile plaques may be associated with memory impairment but not necessarily with dementia.

The quantitative pathologic criteria for AD are age-dependent and reflect the fact that some cortical senile plaques may be a part of normal aging.[1] Our data suggest that the cut-off selected for diagnosing AD in subjects older than 75 years does not distinguish between demented and nondemented subjects. Our future studies will investigate whether a better separation of nondemented and demented subjects can be achieved with particular histologic stains or with neurochemical measures.

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