

The Consortium to Establish a Registry for Alzheimer's Disease (CERAD).

Part II. Standardization of the neuropathologic assessment of Alzheimer's disease

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Article abstract—The Neuropathology Task Force of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) has developed a practical and standardized neuropathology protocol for the postmortem assessment of dementia and control subjects. The protocol provides neuropathologic definitions of such terms as "definite Alzheimer's disease" (AD), "probable AD," "possible AD," and "normal brain" to indicate levels of diagnostic certainty, reduce subjective interpretation, and assure common language. To pretest the protocol, neuropathologists from 15 participating centers entered information on autopsy brains from 142 demented patients clinically diagnosed as probable AD and on eight nondemented patients. Eighty-four percent of the dementia cases fulfilled CERAD neuropathologic criteria for definite AD. As increasingly large numbers of prospectively studied dementia and control subjects are autopsied, the CERAD neuropathology protocol will help to refine diagnostic criteria, assess overlapping pathology, and lead to a better understanding of early subclinical changes of AD and normal aging.

NEUROLOGY 1991;41:479-486

The Consortium to Establish a Registry for Alzheimer's Disease (CERAD), a multicenter study, has developed brief, comprehensive, and reliable clinical and neuropsychological batteries for assessment of patients clinically diagnosed as having probable Alzheimer's disease (AD) as Morris et al¹ recently reported. This current paper reports the subsequent development of a practical standardized protocol for the neuropathologic evaluation of autopsy brains of demented and control subjects. A task force of neuropathologists from nine university medical centers in the United States was formed to achieve the following immediate objectives: (1) to create a neuropathology protocol consisting of an illustrated guidebook and data entry form,² (2) to facilitate the entry of neuropathologic findings into the CERAD information system to be linked with clinical information on demented and cognitively normal subjects, and (3) to establish a mechanism for the continual refinement of the protocol to reflect new technical and scientific developments.

The long-range goals of the protocol are to produce more accurate and reliable neuropathologic criteria for

AD, to determine the neuropathologic spectrum of AD, and to establish the types and frequency of other disorders coexisting with AD or occurring alone. The protocol is not intended to characterize each case definitively. It is designed instead to provide a simple, easily understood, and uniform approach that will indicate levels of diagnostic certainty, reduce subjective interpretation, and assure common language. Consequently, it is particularly valuable as a framework for the documentation of neuropathologic data on "borderline" cases, eg, demented subjects with few neocortical plaques or tangles, or, conversely, nondemented cases with neuropathologic evidence of AD.

To pretest the protocol, neuropathologists from 15 CERAD centers submitted neuropathology data from 142 consecutive brain autopsies on patients clinically diagnosed at their institutions as having probable AD³ and on eight subjects who had no evidence of cognitive impairment or neurologic disease. This report describes the CERAD neuropathology protocol and presents the findings from these 150 autopsies.

* See Acknowledgments on page 485.

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Supported by NIA #AG06790. Dr. Mirra's work is also supported by Veterans Administration Merit Award #5747-4.

Received September 5, 1990. Accepted for publication in final form October 1, 1990.

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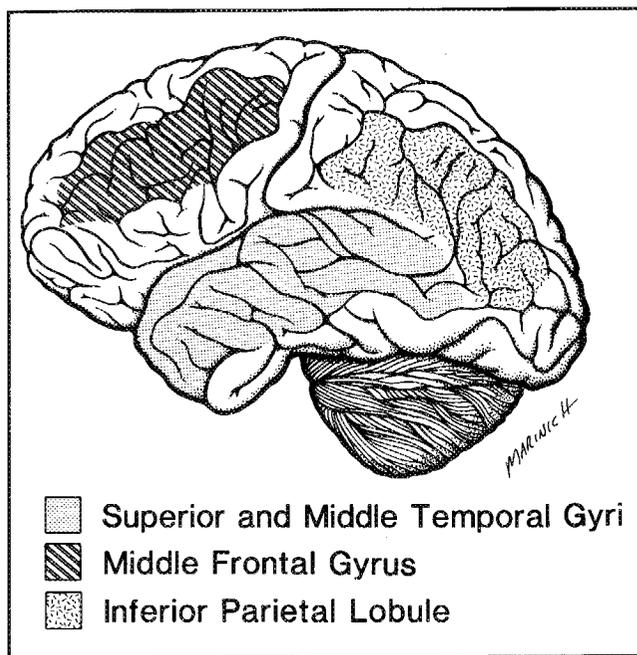


Figure 1. This diagram of the lateral surface of the brain illustrates the areas of neocortex from which recommended neocortical sections are taken.

Methods. *Description of the CERAD neuropathology protocol.* *Gross findings.* The data entry form documents availability of brain and spinal cord tissue, brain weight, and the presence of any gross abnormalities in brain, spinal cord, or meninges. The degree of regional neocortical atrophy and ventricular enlargement, if any, is rated semiquantitatively (none, mild, moderate, severe). The presence or absence of atrophy of the hippocampus and entorhinal cortex as well as pallor of the substantia nigra and locus ceruleus are also recorded. The cerebral blood vessels are examined grossly for atherosclerosis or significant obstruction and aneurysms or other anomalies. The number, size, frequency, distribution, and laterality of lacunar and large infarcts as well as hemorrhages are also recorded.

Microscopic preparations. A minimum of five anatomic regions are designated for microscopic study. Requisite sections include middle frontal gyrus, superior and middle temporal gyri, inferior parietal lobule, hippocampus and entorhinal cortex, and midbrain, including the substantia nigra. Guidelines for the neocortical regions from which the sections are taken are provided (figure 1). Most of the centers participating in this CERAD study routinely sample additional areas of the brain as part of their evaluations.

The neuropathology guidebook recommends that paraffin-embedded sections be cut at a thickness of 6 to 8 micrometers. In addition to hematoxylin-eosin or other general stains, a sensitive silver stain such as the modified Bielschowsky method is recommended for the detection of senile plaques and neurofibrillary tangles. (Use of the Bodian preparation is not recommended.) The fluorescent thioflavine S preparation viewed under ultraviolet light is accepted as an alternative stain for plaques and tangles as well as for cerebral amyloid. The Congo red stain also may be used for evaluating cerebral amyloid. More conventional or traditional histopathologic methods were deliberately recommended as these are used in virtually all neuropathology laboratories. Many laboratories, of course, supplement these techniques with immunocytochemical procedures that may enhance detection of

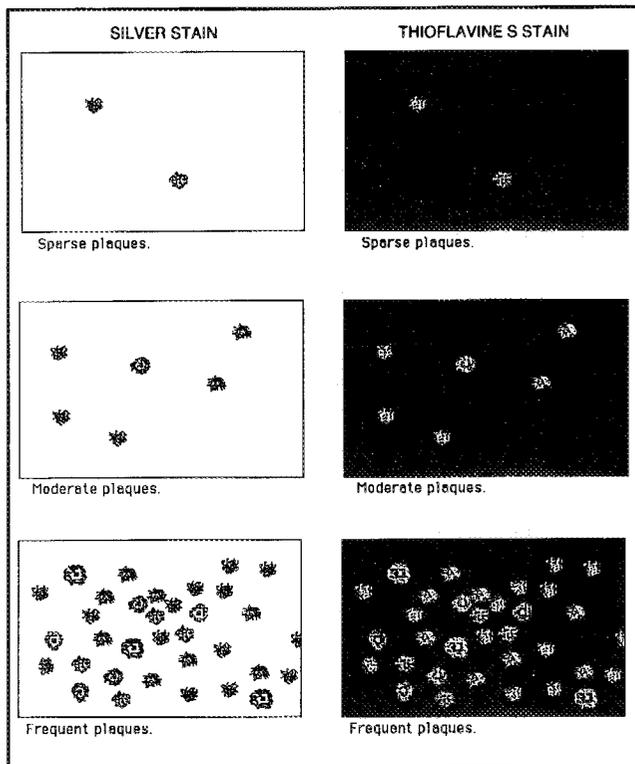


Figure 2. Senile plaques (neuritic) per 100 \times microscopic field. This cartoon provides a guide to semiquantitative assessment of plaque density per square millimeter.

pathologic changes, such as amyloid deposition using beta/A4 antibodies and Lewy bodies using antiubiquitin or other antibodies.

CERAD diagnostic neuropathologic criteria for AD. These diagnostic criteria are based upon the semiquantitative assessment of neocortical senile plaques of the neuritic type, ie, those with thickened silver-positive neurites. Presently, the protocol does not require specification of the number or proportion of diffuse plaques, ie, plaques without discernible abnormal neurites or fibrillar amyloid (also known as "very primitive," "amorphous," or "amyloid"); both neuritic and diffuse plaques label positively with the beta-A4 amyloid protein antibody.⁴⁻¹⁰ The pathogenesis and clinical significance of different plaque types remain controversial. Some neuropathologists believe that diffuse plaques are more commonly encountered in nondemented elderly individuals whereas neuritic plaques are more characteristic of AD⁴; others observe that diffuse plaques are the commonest type encountered in AD.¹⁰ Moreover, the morphologic distinction between plaque type is not always clearcut, and less sensitive staining methods may not detect diffuse plaques.¹¹ Future modifications of the neuropathology protocol will reflect the evolving understanding of the importance of plaque subtype.

The CERAD neuropathologic diagnosis is derived from a three-step process:

Step 1. In order to encourage participation, standardize observations, and avoid time-consuming counts, neuropathologists are first asked to make semiquantitative assessments of the frequency of senile plaques and neurofibrillary tangles in the neocortex in areas of maximum density. The overall degree of vascular amyloid deposition and the proportion of plaques containing amyloid cores are also noted. Micrographs and cartoon illustrations representing examples of mild, moderate, and severe plaque frequencies are provided as guides (figure 2).

Table 1. Age-related plaque scores*

Age of pt at death (yrs)	Frequency of plaques†			
	None	Sparse	Moderate	Frequent
<50	0	C	C	C
50-75	0	B	C	C
>75	0	A	B	C

* An age-related plaque score is determined using patient's age along with plaque frequency in the most heavily affected neocortical section.
 † Based on section of frontal, temporal, or parietal cortex with maximum involvement.

For purpose of this protocol, the letter circled corresponds to the following assessment:

0 = NO histologic evidence of Alzheimer's disease.
 A = Histologic findings are UNCERTAIN evidence of Alzheimer's disease.
 B = Histologic findings SUGGEST the diagnosis of Alzheimer's disease.
 C = Histologic findings INDICATE the diagnosis of Alzheimer's disease.

Step 2. An age-related plaque score is then determined by combining the age of the patient at death and the semiquantitative measure of plaques in the most severely affected region of the neocortex (table 1).

Step 3. This score is then integrated with clinical information regarding the presence or absence of dementia to determine the level of certainty of the diagnosis of AD (table 2). The terms "definite," "probable," and "possible AD" refer here only to the neuropathologic diagnoses and should not be confused with the NINCDS/ADRDA criteria for the clinical diagnosis of AD.³

Evaluation of other pathologic findings. In addition to the gross examination for evidence of cerebrovascular disease described earlier, microscopic features are also assessed. These include the presence and distribution of microinfarcts, white matter pallor without obvious associated vascular disease, and pallor of myelin associated with microinfarcts and arterio-arteriolar sclerosis, a condition sometimes called "Binswanger's disease."

Because changes associated with Parkinson's disease are frequently present in patients with AD,²⁰⁻²² the substantia nigra is evaluated for Lewy bodies, neuronal loss, gliosis, extraneuronal neuromelanin, and neurofibrillary tangles. The frequency of Lewy bodies is scored on a four-tiered system assessing the number of neurons containing one or more Lewy bodies in a single section through the substantia nigra. The presence of Lewy bodies is also determined in other regions such as brainstem and cortex. Although there is no uniformly accepted neuropathologic definition of Parkinson's disease, working definitions were established using the criteria listed in table 3.

Ranking of disorders contributing to dementia. Finally, the pathologist is asked to list all neuropathologic diagnoses and to rank all those considered to have contributed to the dementing process.

Pretest of protocol. The CERAD neuropathology protocol has been pretested by neuropathologists from 15 participating centers. The 150 autopsy brains examined for this purpose were derived from patients in the following three entry groups: *Group 1* consisted of 10 subjects enrolled into CERAD clinical studies with clinical diagnoses of probable AD (nine cases) or as control subjects (one case); in this group, CERAD clinical and neuropsychological batteries had been administered to all subjects. *Group 2* included 133 non-CERAD-

Table 2. Neuropathology diagnosis: Diagnostic criteria for Alzheimer's disease

Normal (with respect to AD or other dementing processes)	a	No histologic evidence of Alzheimer's disease (0 score), and no clinical history of dementia, and absence of other neuropathologic lesions likely to cause dementia
(choose one)	b	An "A" age-related plaque score and no clinical history of dementia
	c	A history of dementia and absence of any neuropathologic lesions likely to cause dementia
Definite		"C" age-related plaque score, and clinical history of dementia, and presence or absence of other neuropathologic lesions likely to cause dementia
CERAD NP probable*		"B" age-related plaque score, and clinical history of dementia, and presence or absence of other neuropathologic disorders likely to cause dementia
CERAD NP possible*	a	"A" age-related plaque score, and clinical history of dementia, and presence or absence of other neuropathologic lesions that could cause dementia
(choose one)	b	"B" or "C" age-related plaque score and absence of clinical manifestations of dementia

* Not to be confused with the NINCDS-ADRDA clinical criteria (McKhann et al, *Neurology* 1984;34:939-944).

The age-related plaque score is integrated with the presence or absence of a clinical history of dementia to arrive at a diagnostic level of certainty with regard to Alzheimer's disease.

assessed individuals for whom the clinical diagnosis of probable AD was made after thorough evaluation by CERAD center-affiliated physicians but not necessarily by using CERAD clinical methods. (These cases were included to provide the opportunity for the neuropathologists to become familiar with the protocol and to insure case material for study during the early phases of this program. As the CERAD longitudinal samples have increased, group 2 subjects are no longer being entered in the database.) *Group 3* included seven non-CERAD-assessed control subjects, ie, individuals over 50 years of age and free of CNS disorders who were examined by experienced physicians at CERAD centers and found to have no evidence of cognitive impairment within a year of death. To avoid bias in case selection, only consecutively accessioned autopsy cases fulfilling the above criteria were accepted.

Analysis of data. All of the completed neuropathology data forms were reviewed by one of us (S.S.M.), and questions concerning the entries were resolved by communication with the appropriate neuropathologists. The data books were then forwarded to the CERAD Data Management Center for entry and analysis.

Table 3. Diagnostic criteria for Parkinson's disease

Definite	a	Presence of Lewy bodies at any site, gliosis, neuronal loss, and depigmented substantia nigra <i>and</i> clinical diagnosis of parkinsonism
(choose one)		Presence of significant degeneration (gliosis, depigmentation, and neuronal loss) of the substantia nigra without Lewy bodies (in the absence of other disorders clearly explaining this change, eg, encephalitis or multisystem degeneration) <i>and</i> clinical history of parkinsonism
	b	
Uncertain		Presence of neuropathologic lesions listed above <i>and</i> absence of clinical diagnosis of parkinsonism

Working definitions of Parkinson's disease are provided to assure uniformity of assessment.

The distribution and frequency of senile plaques and neurofibrillary tangles in cases fulfilling the CERAD neuropathologic criteria for definite AD were analyzed; logistic regression procedures for ordinal data¹² were employed. In addition, as an example of the type of neuropathologic analysis that can be performed using this database, the degree of amyloid deposition in meningeal and parenchymal blood vessels was compared to the proportion of senile plaques containing amyloid cores.

Results. Neuropathologists from 15 centers submitted data on autopsy brains of 142 patients clinically diagnosed as having probable AD and eight nondemented control subjects (table 4) from groups 1 to 3 as described above. In general, the neuropathologists readily accepted the data forms and found them to be straightforward and relatively easy to use. Most of the neuropathologists reported that using the form for entry of the neuropathologic information did not add substantively to the time ordinarily spent in working up these cases.

The neuropathologic findings on the patients clinically diagnosed as having probable AD are summarized in table 5. Using CERAD neuropathology diagnostic criteria, neuropathologists determined the primary dementing illness to be definite AD in 119 of the 142 cases (83.8%). Another 13 cases (9.1%) were judged to have probable or possible AD. (One case showing only neurofibrillary tangles, striatal degeneration, and no senile plaques was characterized by the referring neuropathologist as "atypical AD," but this case does not fall within CERAD neuropathologic criteria for AD.) Thus, 132 of 142 cases (or 93%) displayed AD changes listed by the neuropathologist as the primary cause of dementia. Parkinson's disease changes were encountered in 27 (23%) of the cases with definite AD. Although some degree of cerebrovascular disease was found in about one-third of the cases with definite AD, only three patients (2%) were considered to have vascular disease as the primary cause of their dementia. The neuropathologic diagnoses in these three cases

Table 4. Distribution of demented and control subjects by age and sex

	Subjects		Age (yrs)	
	No.	Percent	Mean	Range
Demented				
Men	77	54.2	73.2	49-94
Women	65	45.8	79.9	59-95
Total	142		76.3	49-95
Controls				
Men	5	62.5	65.8	56-79
Women	3	37.5	64.0	59-70
Total	8		65	56-79

were, respectively, Binswanger's disease, multiple infarcts, and chronic vasculitis. Neuropathologists interpreted the major cause of dementia in five individual cases to be, respectively, Pick's disease, lobar atrophy, progressive supranuclear palsy, cortical degeneration of unspecified type, and corticonigral degeneration. However, these cases of cortical and corticonigral degeneration also had some degree of concomitant AD pathologic change, emphasizing the complexity of interpretation and the need for reliable data when overlapping pathologies occur. No morphologic basis for the dementia was found in one case.

In the cases fulfilling CERAD neuropathologic criteria for definite AD, there were no significant differences in the frequency of senile plaques in the three neocortical regions. We also compared the degree of deposition of vascular amyloid with the proportion of amyloid-cored plaques in neocortex. In the frontal sections, the degree of amyloid deposition in the meningeal and parenchymal blood vessels correlated positively ($p < 0.002$ and $p < 0.02$, respectively) with semiquantitative estimates of the proportion of plaques containing amyloid cores. That is, brains of patients with AD who had a high proportion of amyloid core-containing plaques often showed heavy amyloid deposition in cerebral vessels, whereas those with few to no amyloid cores in plaques tended to have little to no vascular amyloid.

The control brains from the eight subjects without cognitive impairment revealed a spectrum of findings (table 6). Three of the eight control cases showed no plaques, tangles, or amyloid angiopathy. The brain of a 69-year-old control subject with carcinoma of the colon displayed sparse neocortical plaques giving an age-related plaque score of B (table 1), ie, histologic findings suggest the diagnosis of AD. The brain of a 70-year-old nondemented patient with squamous cell carcinoma displayed frequent frontal cortical plaques giving an age-related plaque score of C, ie, histologic findings indicate the diagnosis of AD. In the absence of a clinical history of dementia, both cases were classified as possible AD (type b) using CERAD neuropathology criteria summarized in table 2. One other control case had a single neurofibrillary tangle in the temporal cortex, sparse tangles in the hippocampus and entorhinal cortex, and sparse meningeal vascular amyloid. Another brain showed only sparse tangles in the hippocampus

Table 5. Summary of neuropathology diagnoses on 142 cases clinically diagnosed as probable Alzheimer's disease

Primary dementing illness*	No. of cases	Parkinson's disease (PD) changes	Cerebrovascular disease	Concomitant diagnoses made (no. of cases)
Definite AD	119 (84%)	27 (23% of definite AD cases)	40 cases† (34% of definite AD cases)	Binswanger's‡ (1); definite PD‡ (5); uncertain PD (19‡); Lewy body disease (5‡); lacunes (12‡); infarcts—all sizes (26‡); vascular malformation (1); petechial hemorrhages (2); meningioma (2); metastatic Ca (1); Guillain-Barré (1); chronic subdural hematoma (1); old subarachnoid hemorrhage (1); meningitis (2), caudate atrophy (1); abscess (1), hippocampal sclerosis (1)
Probable AD	10 (7%)	3	0	Uncertain PD (1); Lewy body disease (1‡); definite PD (1‡)
Possible AD	3 (2%)	0	1	Lacunes and infarct (1); hydrocephalus (1‡)
"Atypical AD"§	1	0	0	
Cerebrovasc. disease Infarcts and lacunes (1) Chronic vasculitis (1) Binswanger's dis. (1)	3 (2%)	0	3	Normal pressure hydrocephalus‡ Possible AD‡ Probable AD
Cortical degeneration, unknown etiology	1	0	0	
Corticonigral degeneration	1	0	1	Definite AD‡; infarct
Progressive supranuclear palsy	1	1	0	Uncertain PD‡
Pick's disease	1	0	0	
Lobar atrophy	1	0	0	Possible AD
Normal brain	1	0	0	N/A
Total cases	142	31	45	

* As rated by the neuropathologist (see table 2 for neuropathology definitions).
† Includes all lacunes, infarcts, microinfarcts, and Binswanger's disease; does not include amyloid angiopathy or petechial hemorrhages.
‡ Judged by the neuropathologist to have also contributed to dementia in at least some of the cases.
§ Just tangles (no plaques) and striatal degeneration.

and entorhinal cortex without plaques or amyloid angiopathy. Amyloid angiopathy alone was found in an additional control case without plaques or tangles.

Discussion. *The need for standardization of the neuropathology assessment in AD.* Inconsistencies in the neuropathologic assessment of AD have long been recognized. No agreement exists at this time, and the need for standardized diagnostic criteria has become apparent. In an effort to meet this need, a panel of neuropathologists in 1985 recommended using quantitative criteria based upon absolute age-related neocortical

plaque counts.¹³ Four years later, however, a survey of 104 neuropathologists in the United States and Canada showed that only 21% of the respondents actually applied these criteria to their cases.¹⁴ Tierney et al¹⁵ stated in their pathologic criteria for the clinical diagnosis of probable AD that, "in spite of consistency in the application of clinical criteria, the lack of agreement caused by differing neuropathologic criteria for Alzheimer's disease limits our ability to compare research protocols that use different neuropathologic criteria." Although it is not the intention of CERAD to impose any absolute diagnostic criteria, our protocol addresses this problem

Table 6. Summary of clinicopathologic features on eight control cases

Clinical diagnosis	Age	Sex	Race	Plaques	Tangles	Vascular amyloid
Carcinoma of the colon; enrolled in AD study as control patient; lucid correspondence from patient 7 mos before death	69	Male	White	Sparse in neocortex, hippocampus, amygdala; moderate in entorhinal cortex	Sparse in hippocampus and entorhinal cortex; none in amygdala	None
Squamous cell carcinoma of esophagus; alert and oriented 1 mo before death	56	Male	Black	None in neocortex, hippocampus, entorhinal cortex; amygdala not examined	None in neocortex, hippocampus, entorhinal cortex; amygdala not examined	None
Squamous cell carcinoma; normal mental status described immediately before death	70	Female	Black	Frequent* in frontal cortex; moderate in temporal and parietal cortex; sparse in entorhinal cortex; none in hippocampus	None	None
Rheumatoid arthritis; chronic emphysema; cognitively normal on testing 3 mos before death	64	Male	White	None	None	Sparse to moderate parenchymal and meningeal deposition hippocampus, amygdala, and neocortex
Acute myelomonocytic leukemia; alert and oriented when seen by neurologist 2 mos before death	61	Male	White	None	None	None
Metastatic large cell carcinoma of lung	59	Female	White	None	None	None
Ameloblastoma of mandible metastatic to liver and lungs	63	Female	White	None	Sparse in hippocampus and entorhinal cortex	None
Carcinoma of pancreas and metastasis to brain	79	Male	White	None	Sparse in hippocampus, entorhinal cortex, and temporal cortex	Sparse meningeal amyloid

* Most small primitive plaques.

by offering a uniform method for the neuropathologic assessment of AD.

There is no doubt that variation exists among neuropathology laboratories regarding both histologic techniques and interpretation used to assess AD. In surveying CERAD neuropathologists, we learned that 15 centers used seven different staining techniques on brain tissue sections ranging from 6 to 15 micrometers in thickness. Even when common stains are used (such as the Bielschowsky method), modifications abound. In many laboratories, specific staining techniques are a virtual tradition; technicians and pathologists alike feel comfortable in their use and interpretation. Although brain tissue riddled with neocortical neuritic plaques probably would present no diagnostic problem to any of the participating neuropathologists, we believe that differences in technique and interpretation of the morphologic findings may yield disparate inter-center data and conclusions.

This notion was strengthened by the survey by

Wisniewski et al.¹⁴ They tabulated the diverse methodologic and interpretive approaches used by 104 neuropathologists in evaluating cases clinically diagnosed as AD. Methods listed by respondents included some Bielschowsky method (51%) and thioflavine S staining (13%), although 42% used other silver or amyloid preparations. This methodologic inconsistency was paralleled by variation in methods of evaluation of observations. Most of the neuropathologists did not use a strictly quantitative assessment to make the diagnosis of AD. Moreover, there was much variation in the extent to which they incorporated the clinical information in their diagnostic evaluation.

In an earlier position paper, Ball¹⁶ made a similar point regarding the variations in methodology used in the assessment of AD. He stated "optimal comparison of quantitative data in the neuropathological diagnosis would involve the standardization of various fixation, processing, and staining techniques used by participating laboratories. Considerable debate persists about the

best type of histological method to show the various Alzheimer lesions. This goal could be achieved, but only with a large amount of planned cooperation." Indeed, the literature is replete with observations based upon varying methodologies. The CERAD neuropathologists are concerned about intercenter variation in staining technique and interpretation and are currently completing a standardization study addressing this important issue.¹¹

Potential uses of the CERAD neuropathology protocol. The CERAD neuropathology protocol was designed to create a database that has many potential uses, including the refinement of diagnostic criteria, the assessment of overlapping and coexistent pathology, and the understanding of early changes in AD.

Refinement of diagnostic criteria. The inclusion of a wide range of neuropathologic data correlated with clinical information provided by the CERAD clinical batteries may allow refinement of diagnostic criteria. For example, as suggested by Tomlinson,¹⁷ other more reliable diagnostic indicators may be found, eg, entorhinal or brainstem neurofibrillary tangles. The flexibility of the CERAD neuropathology protocol will enable us to take advantage of new or improved histopathologic, immunocytochemical, or other techniques.

Heterogeneity. A large-scale longitudinal study like CERAD should be well equipped to deal with the issue of clinical and neuropathologic heterogeneity in AD. Clinical features such as extrapyramidal signs or early versus late language impairment may be paralleled by distinctive patterns of neuropathology. Mayeux et al¹⁸ and Chui et al¹⁹ described a substantive subset of AD patients with extrapyramidal signs in the absence of neuroleptics along with severe intellectual and functional decline. These workers stressed the need for pathologic correlation but, thus far, such correlative studies have been limited. Some investigators have suggested that extrapyramidal signs in AD, especially rigidity, are related to coexistent Parkinson's disease pathology²⁰⁻²²; Morris et al,²³ however, have found heterogeneous pathologic correlates of clinical parkinsonism in AD.

Data on extrapyramidal signs are recorded in the CERAD clinical assessment forms and will be correlated with information in the neuropathology protocol on the substantia nigra as well as the presence and distribution of Lewy bodies. Such correlations will permit us to look at clinical and neuropathologic correlates of Parkinson's disease changes, either coexisting with AD pathology or occurring alone. The CERAD neuropathology protocol also may answer questions about so-called "diffuse Lewy body disease" often seen in the clinical and neuropathologic setting of AD²⁴ and may establish whether or not such cases represent a clinically distinctive variant of AD.²⁵

The CERAD protocol will provide valuable data on the controversial role of cerebrovascular disease in dementia patients. Estimates of the percentage of dementia patients with significant cerebrovascular disease vary^{26,27} and have been estimated as being as high as one-third.²⁸ Some workers maintain that patients diagnosed as having multi-infarct dementia or a combina-

tion of vascular disease and AD show predominantly AD or mixed neuropathology^{27,29}; postmortem studies revealed a diagnostic accuracy of the clinical diagnosis of vascular dementia as 85% in a Finnish study of demented patients by Erkinjuntti and coworkers.³⁰ However, in a neuropathologic study of patients clinically diagnosed as having AD, Joachim et al³¹ found that only two of 150 cases showed a purely vascular basis of dementia.

Although the CERAD database will include only those patients clinically diagnosed as having probable or possible AD,³ it will provide information on the extent to which vascular disease coexists with or mimics AD. The neuropathology data form was designed to include information on the size, location, and nature of the gross and microscopic vascular lesions to help resolve some of these questions. This will be particularly valuable when combined with data obtained using the CERAD neuroimaging protocol currently in development.

Early changes of AD. Correlation of CERAD clinical and neuropsychological findings with the distribution of AD changes in patients with mild dementia or short duration of symptoms and in nondemented control subjects may reveal hierarchical patterns in the nature or in the distribution of early neuropathologic changes. In an attempt to provide clues to these early changes, neuropathologic findings in autopsies of relatively young patients with Down's syndrome have been described.³²⁻³⁴

Most of the patients entered into the CERAD clinical protocol, however, will be in the more advanced stages of AD by the time of death. Berg et al³⁵ emphasized the rapidity with which most AD patients move from the stage of mild to moderate or severe dementia. It is likely, therefore, that we may be largely dependent upon follow-up of CERAD control subjects as a source of early dementia cases.

Note: Requests for information about CERAD and its copyrighted assessment batteries should be directed to Albert Heyman, MD, Duke University Medical Center, Box 3203, Durham, NC 27710.

Acknowledgments

In addition to the authors, the following individuals provided helpful input into the development of the neuropathology protocol and contributed data from case material to the CERAD data bank: Melvyn J. Ball, MD, University of Western Ontario, London, ON, Canada; Linda M. Bierer, MD, Bronx VA Medical Center, New York, NY; Diana Claassen, MD, University of Pittsburgh, Pittsburgh, PA; Lawrence Hansen, MD, University of California at San Diego, La Jolla, CA; Michael Hart, MD, University of Iowa, Iowa City, IA; John Hedreen, MD, Johns Hopkins Hospital, Baltimore, MD; Victor Henderson, MD, University of Southern California, Los Angeles, CA; Bradley T. Hyman, MD, PhD, Massachusetts General Hospital, Harvard University, Boston, MA; Catharine Joachim, MD, Brigham and Women's Hospital, Harvard University, Boston, MA; William Markesbery, MD, University of Kentucky, Lexington, KY; A. Julio Martinez, MD, University of Pittsburgh, Pittsburgh, PA; Ann McKee, MD, Massachusetts General Hospital, Harvard University, Boston, MA; Carol Miller, MD, University of Southern California, Los Angeles, CA; John Moossy, MD, University of Pittsburgh, Pittsburgh, PA; David Nochlin, MD, University of Washington, Seattle, WA;

Daniel Perl, MD, Mt. Sinai Medical Center, New York, NY; Carol Petito, MD, Cornell Medical Center, New York, NY; Gutti R. Rao, MD, University of Pittsburgh, Pittsburgh, PA; Robert L. Schelper, MD, University of Iowa, Iowa City, IA; Ursula Slager, MD, University of Southern California, Los Angeles, CA; and Robert D. Terry, MD, University of California at San Diego, La Jolla, CA.

The authors thank John Morris, MD, and Gerda Fillenbaum, PhD, for thoughtful review of the manuscript and Sylvia Wrobel, PhD, and Florence Nash for editorial assistance. Duane Beekly helped with data management. Jan Fowler and Mary Strickland provided fine administrative and secretarial support and Adina Alazraki assisted with the computer-generated graphics.

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