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Consortium to Establish a Registry for Alzheimer's Disease (CERAD): The first twenty years

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Abstract The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) was funded by the National Institute on Aging in 1986 to develop standardized, validated measures for the assessment of Alzheimer's disease (AD). The present report describes the measures that CERAD developed during its first decade and their continued use in their original and translated forms. These measures include clinical, neuropsychological, neuropathologic, and behavioral assessments of AD and also assessment of family history and parkinsonism in AD. An approach to evaluating neuroimages did not meet the standards desired. Further evaluations that could not be completed because of lack of funding (but where some materials are available) include evaluation of very severe AD and of service use and need by patient and caregiver. The information that was developed in the U.S. and abroad permits standardized assessment of AD in clinical practice, facilitates epidemiologic studies, and provides information valuable for individual and public health planning. CERAD materials and data remain available for those wishing to use them.

Keywords: Consortium to Establish a Registry for Alzheimer's Disease; CERAD; Alzheimer's disease; Clinical assessment; Neuropsychological assessment; Neuropathological assessment; Norms; Prevalence; Incidence

1. Background

Dementing disorders have long been recognized [1], with the identification of Alzheimer's disease (AD) typically dated back to the century-old paper by Alzheimer [2]. Although considerable attention has been paid to AD and substantial progress has been made in identifying its characteristics, nevertheless, much remains unclear. As diagnos-

With the exception of the senior author (Dr Heyman), who was the Principal Investigator of CERAD, and the first author, who was the Project Director, the order of authorship reflects the order of development of CERAD's primary assessments. The Methodology and Data Management Center (Dr van Belle) and the Clinical (Dr Morris) and Neuropsychology (Dr Mohs) batteries were developed simultaneously. These were followed by the Neuropathology protocol (Dr Mirra), the Neuroimaging protocol (Dr Davis), the Behavior Rating Scale for Dementia (Dr Tariot), evaluation of family history (Dr Silverman), and structured assessment of extrapyramidal dysfunction in AD (Dr Clark).

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tic procedures improve, the complexities of this disease become more apparent, and the threat it imposes becomes increasingly evident. In the population 65 years of age and older, both the incidence and prevalence of this disorder double every succeeding 5 years [3], with estimated prevalence as high as 40% among those older than the age of 85. AD, not recognized as a leading cause of death in 1980, was recognized as the fifth leading cause of death in 2003 among persons 65 years of age and older [4].

There is presently no cure and inadequate amelioration for this condition. It can not only strip personality and capability, but it is demanding on family members, seriously disrupting their lives and their work. It is expensive for the long-term care system, where about half of the residents might suffer from dementia, a substantial proportion of whom can no longer afford their own care. Although people are now reaching their older years in better health [5,6], it remains to be seen whether there will be a decrease in the incidence of AD. Currently the fastest growing element of the population is among those 85 years of age and older, the age group in which the incidence of AD is greatest.

A major step in the management of a disease lies in accurate diagnosis. Relevant to current work, clinical diagnostic criteria for dementia and AD were specified about 25 years ago and then further refined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) [7–9], the International Classification of Diseases [10,11], and the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) [12]. Neuropathologic criteria for AD were proposed by Khachaturian [13] in 1984.

None of these clinical diagnostic criteria specified how the behaviors at issue were to be examined. While working within the general guidelines that these criteria present, different investigators could legitimately use very different measures or the same measures but with different cut points to reach a diagnosis. Each investigator could be right within the parameters chosen, but there might be little agreement across investigators. Indeed, comparison of these alternative clinical diagnostic criteria showed little agreement in identifying dementia [14], and a review of studies of the prevalence and incidence of AD carried out by the U.S. General Accounting (now Accountability) Office excluded a major U.S. survey because it appeared to be a substantial outlier [15]. Comparing or aggregating information under such circumstances has questionable legitimacy, and progress is hindered.

In 1986 the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) was funded by the National Institute on Aging (NIA) to address such concerns. Its mandate was to develop standardized, reliable, and valid assessments of AD for use by all Alzheimer Disease Centers (ADCs) established by the NIA, provide training in their use, and aggregate CERAD-based data from carefully evaluated patients and controls. Ultimately, CERAD developed standardized and validated clinical, neuropsychological, and neuropathologic assessments that were used by the ADCs [16,17]. CERAD also prepared a standardized protocol for neuroimaging in AD but did not promote it because intersite agreement on the rating of these neuroimages was considered to be inadequate [18]. Additional evaluated assessments that were developed included a Behavior Rating Scale for Dementia to assess psychopathologic behavior in AD [19,20], a family history assessment for investigators interested in familial aggregation studies and the possible genetics of AD [21], and because parkinsonism might be manifest with AD, a scale to assess extrapyramidal dysfunction [22]. CERAD also prepared information for ADCs to use to facilitate brain donation and simply written educational material in English and Spanish describing the early symptoms of AD and the appropriate steps to take to handle this condition (Table 1).

Here we briefly describe each of the batteries and scales, the training procedures used, and the development of a database. We also touch on the many uses occasioned by the availability of these measures. These include use in the clinic, in epidemiologic surveys, and in drug intervention trials. The data are relevant for planning at the individual and public health levels. Norms have been developed for clinic patients, community residents, and various racial/ethnic groups, and the measures have been translated into the major European and Asian languages (with further validation in several of these), permitting international comparison. The availability of the measures and the development of a clean, substantial, and accessible database have facilitated identification of possible clinical, neuropsychological, and neuropathologic subtypes of AD and determination of the characteristics of natural disease progression. It has also encouraged the development of statistical procedures appropriate for handling complex longitudinal data.

2. Organization of CERAD

Organizationally, CERAD consisted of three critical elements: an administrative core, headed by the principal investigator, who supervised the entire project; a methodology and data management center, which, among other activities, constructed all the data gathering forms, developed data input procedures, encouraged participating sites to abide by the protocol-prescribed follow-up evaluation intervals, and handled data cleaning and analyses; and a series of task forces, each headed by an acknowledged specialist in the area of interest, and external advisory committees. In developing their assessments, the task forces focused on measures that were basic to the assessment of AD, familiar, and brief. Underlying CERAD's success was the invaluable collaboration with each participating site, where those engaged included the site director (typically a

Table 1
Main CERAD instruments and ancillary materials

Instrument	Brief description of contents
Clinical battery	Demographic data on subjects and informants; clinical history; Blessed Dementia Rating Scale, end points in late stage dementia, screen for Behavior Rating Scale for Dementia (patients only); Short Blessed; calculation, clock, language; physical exam; neurologic exam – overall and extrapyramidal dysfunction; report of laboratory and neuroimaging studies; Clinical Dementia Rating scale; diagnostic impression including AD, AD with secondary contributing disorder, extrapyramidal dysfunction in AD; non-AD dementias
Neuropsychology battery	Verbal Fluency (animal naming), Boston Naming (15 items), Mini-Mental State Exam (serial 7s omitted), Word List Learning, Constructional Praxis, Word List Recall, Word List Recognition (10 original words, 10 foils), Constructional Praxis recall
Neuropathology battery	Demographic data; history; gross examination; cerebrovascular disease, gross findings; microscopic vascular findings; major nonvascular microscopic findings; microscopic evaluation; hippocampus, neocortex; assessment of neurohistologic findings; neuropathologic diagnosis; final assessment
Neuroimaging battery	Technical protocol on acquisition of MR scans; general information; cerebral atrophy (perceptual ratings); white matter lesions, excluding hemorrhages and infarcts; cerebral vascular disease (infarcts and lacunes, parenchymal hemorrhages). Extensively illustrated.
Behavior Rating Scale for Dementia	46-item scale assessing presence and frequency of behaviors on 6 subscales: depressive symptoms, inertia, vegetative symptoms, irritability/aggression, behavioral dysregulation, psychotic symptoms. An abbreviated 17-item scale has also been developed. Scales, manual, training video, and scoring guide available.
Family history assessment	Mapping of first- and second-degree kin and determining likely presence of AD, Parkinson's disease, and Down syndrome
Services assessment	Evaluation of in-home and community-based service use and need, including institutionalization and hospitalization. Material not fully evaluated.
Autopsy resources	Materials to facilitate autopsy recruitment by sites (guidelines, forms, sample letters, informational brochures)
Educational brochures	Information on early symptoms of AD and steps to take, in 6th-grade level English and simple Spanish

clinician), administrative and data entry personnel, neuropsychologist and psychometrician, neuropathologist and neuroimaging specialists, as well as faculty with particular interests in areas such as genetics. Throughout the CERAD years, participating sites were kept informed by newsletters, mailings, fax, telephone, and, as technology advanced, by e-mail, in addition to face-to-face meetings, typically held at the annual meetings of professional societies. Starting with 15 ADCs, eventually 29 university sites and nine special focus sites (eg, high minority enrollment, non–English-speaking) were eligible to submit data on patients with AD and control subjects who met inclusion/exclusion criteria.

The clinical and neuropsychology task forces were the first to be established. After the successful development of the clinical and neuropsychology batteries, additional task forces to address neuropathology and neuroimaging were created. As interest increased and need was recognized, subtask forces, affiliated with the clinical task force, were instituted to develop evaluated assessments for behavioral pathology, extrapyramidal dysfunction, and family history. Finally, CERAD broadened its scope yet further to include consideration of the noninstitutional services used and needed by patients with AD and their caregivers.

At the encouragement of NIA and with international interest, measures (in particular, the clinical and neuropsychological batteries and the Behavior Rating Scale for Dementia) were translated. After the successful development and increasing use of the CERAD measures, consideration turned to broadening the clinical scope of CERAD to include a broader array of dementias and, in particular, to examine dementia in its very early stages.

3. Eligibility of subjects for the CERAD database

Entrants had to be 50 years of age or older. No maximum age was set. AD patients had to meet NINCDS/ADRDA criteria [12] modified in two ways: memory loss had to be for a minimum of 12 rather than 6 months, and age could be older than 90 years. Probable AD patients were not permitted to have other health conditions that could contribute to dementia (ie, no history of stroke; severe hypertension; Parkinson's disease; serious renal, metabolic, or toxic disorders; major neurologic illness; alcoholism; cardiac disease; etc). Some cases of possible AD were accepted where other potentially contributing disorders were present, but AD was judged to be the primary cause of dementia. Patients had to be cooperative, ambulatory, understand and speak English (or the language of testing), and have no sensory disorder that precluded testing. Initially, score on the Mini-Mental State Examination (MMSE) [23] had to fall between 10 and 24 or between 6 and 24 on the Short Blessed Test [24]. The lower levels were relaxed later to permit inclusion of more impaired patients, as long as they could respond to at least two of the neuropsychology measures. Patients had to have an informant or caregiver who knew them well and could report observations confirming that the patient had experienced cognitive and functional decline relative to premorbid abilities. Patient characteris-

tics were checked closely to ensure compliance with entry requirements. Thus, CERAD patients represent a very "clean" group with AD. Control subjects had to meet the same standards as patients with the exception of the MMSE/Short Blessed criteria; they could show no evidence of dementia and could not be the kin of a patient. To reduce potential site effects, sites were initially limited to submitting 40 cases and 30 control subjects.

All measures were administered to both cases and controls, with the exception of the informant-derived Blessed Dementia Rating Scale [25]. Controls were not required to have informants. In longitudinal analysis this facilitated identification of changes caused by disease as compared with those attributable to aging. Sites were expected to gather data annually, but some were more attuned to this than were others, as indicated by variable dropout. Dropout also varied by race [26] and by severity of disease; the less severely impaired were more likely to drop out [27].

4. Data available

The clinical and neuropsychological batteries were administered to 1,094 patients with AD (890 white, 204 black) and 463 control subjects (429 white, 34 black). Of these entrants, 197 cases and 38 controls provided only baseline data, whereas 639 cases and 368 controls were evaluated on three or more annual occasions, with some followed for up to 8 years. During the course of the study 47% of the patients, but only 4% of the controls, entered a nursing home, and 411 patients and 25 control subjects died. Brain autopsy data were available on 202 patients and 8 controls. De-identified clinical, neuropsychological, and neuropathologic information on these subjects is on deposit at the National Alzheimer's Coordinating Center at the University of Washington (www.alz.washington.edu). The database, batteries, and additional material are also available on CD from the CERAD administrative office (http://cerad.mc.duke.edu).

4.1. Uses of the database

The CERAD database was developed before the major advent of antidementia agents. Few enrolled in CERAD took such drugs (those who did were noted). Thus, the CERAD data provide an ethical control group, making it possible to examine the natural history of AD and possibly helping to determine the impact of pharmacologic or other interventions (there are, however, problems associated with the use of historical control groups). In regard to the natural history of AD, articles have been published on depression, insight, weight change, the time needed to reach selected end points (and their stability), and transition time from one stage to another [28–32]. The clock drawing test is one of a set of brief objective measures included in the clinical battery to facilitate the clinical diagnosis of AD without reliance on the neuropsychological test results, thus permitting the neuropsychology battery to be evaluated independently. CERAD's straightforward scoring of this measure (clocks are scored on a 4-point scale: normal, mild, moderate, severe impairment, with examples provided for each level) has been found to be reliable and has been included in brief screens of dementia [33].

5. Battery content, reliability, and validity

Table 1 provides an outline of the information gathered by each measure.

5.1. Clinical assessment

The clinical battery sought information in areas relevant to determination of dementia and AD, doing so without recourse to information on the neuropsychology battery to permit independent assessment of each. To ensure that information was obtained and scored in a uniform manner across sites, an instruction manual detailed the diagnostic criteria, use of the clinical and neuropsychological batteries, and the scoring of the measures [16]. In addition, training for site clinicians was held at the annual meetings of the American Academy of Neurology and the American Neurological Association. Videotaped gold standard cases evaluated with the clinical battery were shown, and administration and scoring were discussed and reviewed to ensure common agreement. Sites were permitted to enter data into CERAD only after submitting videotaped assessments of cases that were reviewed and approved by the chairs of the clinical and neuropsychological task forces.

At the sites, forms completed on patients and controls selected for CERAD were entered electronically in a double data entry system that was programmed to check for out-of-range values and reduce missing entries. Special attention was paid to the staging of dementia severity with the Clinical Dementia Rating [34]. The entire scale with full descriptors was included to improve agreement on use [35].

The validity of the clinical assessment was determined with neuropathologic diagnosis as the gold standard. Examination of autopsy brains derived from 201 patients clinically diagnosed as having probable or possible AD confirmed the diagnosis of AD as the primary dementing illness in 176 decedents (87.6%). In this group of confirmed AD cases, coexistent cerebrovascular lesions were present in 32% and concomitant pathology of Parkinson's disease (PD) in 23%. The primary dementing disorders present in the remaining 25 patients included PD-related pathology (n = 9), hippocampal and entorhinal sclerosis (n = 4), miscellaneous neurodegenerative and other disorders (n = 6), and no significant changes (n = 6) [36]. Thus, in a multisite setting that included experienced neurologists, the clinical diagnosis of AD based on the CERAD clinical battery (without reliance on the neuropsychological test results) was found to have substantial accuracy. At the same time it was obvious that concomitant pathologies could be present

with AD, and that at least in some cases, clinically identified AD might be attributable to other conditions.

5.2. Neuropsychological assessment

The neuropsychology measures chosen were those recognized as assessing cognitive functions implicated in AD. Although the original intent was to permit staging of AD, later study found that some of the measures, in particular delayed recall of the word list, could efficiently distinguish persons with dementia from those with normal cognition.

To facilitate administration and scoring of the neuropsychology measures, directions for administration, if brief, were printed directly on the scoring page. If longer, they were printed on the facing page, together with explicit information on scoring. In addition, a training video was prepared (in English and French), demonstrating appropriate administration of the neuropsychology measures. Before permitting sites to enter data, they had to submit acceptable audio recordings and correctly scored hard copy of two cases. Spot checks were carried out throughout the study by selecting five entries at random each month and rescoring them. Modifications needed were transmitted to the sites. Few problems occurred.

One-month test-retest reliability was determined on the basis of data from 632 patients with mild or moderate AD and 394 control subjects. For AD patients, correlations ranged from 0.80 to 0.91 for verbal fluency, abbreviated Boston Naming, MMSE, Word List Learning, and Constructional Praxis. Correlations were lower for Word List Recall ($r = 0.56$) because of a floor effect and for Word List Recognition (original words: $r = 0.53$; foils: $r = 0.60$) because of ceiling effects. Test-retest reliability was not determined for Constructional Praxis Recall, because it was a later addition to the battery. On all measures, correlations were lower for control subjects than for AD patients because of ceiling effects [37]. Inter-rater reliability was high, with intraclass correlation coefficients ranging from 0.92 (Constructional Praxis) to 1.0 (Word List Recall) [16].

In regard to validity, cross-sectionally, average level of performance was poorer as stage of AD increased, with some measures reaching floor before others [38]. These findings have been confirmed in nonclinical settings and by other investigators [39]. Decline in performance was also identified longitudinally; the rate of decline depended on initial level of performance [40].

5.3. Neuroimaging assessment

Considerable attention was given to developing standardized procedures for administering and scoring magnetic resonance imaging (MRI) in AD and in modifying the protocol in response to pre-testing. Nevertheless, inter-rater agreement among 14 raters rating 28 MRI scans of elderly patients was, overall, disappointing. Accordingly, although the protocol is available, it has not been recommended for use in multicenter studies, although use at any one site might be satisfactory [18]. More sophisticated means of evaluating neuroimages have since been developed, which should produce improved agreement across sites. Nevertheless, use in one study of 20 CERAD patients with neuropathologically ascertained definite AD found a significant correlation between neuroimaging evidence of temporal horn enlargement and autopsy-identified hippocampal atrophy, as well as between severity of cerebral atrophy determined by neuroimaging and MMSE score closest in time to the scan [41].

5.4. Neuropathology assessment

The components of the neuropathology assessment are indicated in Table 1. Required microscopic sections included hippocampus and amygdala as well as frontal, temporal, parietal, and occipital neocortex. Because previous work indicated that quantitative assessment was problematic, CERAD neuropathologists opted to use a semiquantitative approach for assessing the frequency of senile plaques (neuritic and diffuse), neurofibrillary tangles, and other changes. The semiquantitative assessment of the frequency of neuritic plaques was related to patient age. Together with clinical history, this age-related plaque score indicated levels of certainty of the diagnosis of AD, ie, definite, probable, or possible AD or no evidence of AD. To facilitate accurate neuropathologic diagnosis of AD, a primer for pathologists was published [42]. Neuropathologists were asked to apply the routine stains of their choice to these sections and to assess each case by using semiquantitative and quantitative measures. There was good inter-rater agreement on the relative severity of AD cases, and agreement on plaque and tangle frequencies was significantly greater for semiquantitative than quantitative assessment.

The CERAD guidelines have been recommended by the Autopsy Committee of the College of American Pathologists [43,44] and form a basis for the consensus guidelines on the autopsy diagnosis of dementia with Lewy bodies [45]. A consensus conference held jointly by the NIA and the Reagan Institute largely adopted the CERAD system but also upgraded the significance of neurofibrillary tangle distribution and frequency in reaching a level of likelihood that AD accounts for the dementia [46].

Among the CERAD batteries, the neuropathology protocol is the one most cited and might be the one most used. It has been critically compared with the Braak and Braak [47], Khachaturian [13], NIA–Reagan Institute [46], and the Tierney A3 criteria [48–51]. The CERAD neuropathology criteria have been and continue to be used in a substantial number of studies, both in the U.S. and abroad.

Some have expressed concerns that the CERAD protocol fails to take into account significant pathologic and biochemical factors such as estimations of soluble amyloid load, aberrant tau accumulation, and synaptic density [52].

The protocol has not been modified to encompass changes reflecting our latest understanding of certain other dementias (eg, frontotemporal dementias, dementia with Lewy bodies, and vascular dementia). Although the CERAD protocol requires documentation of gross and microscopic changes of cerebrovascular disease, the significance of any vascular pathology is not assessed. Finally, unlike other CERAD batteries, the neuropathology battery has not been translated, because most users have a working knowledge (or better) of English, and no response is required of subjects.

6. CERAD's limitations

In common with other studies, CERAD also has limitations. A preferred sampling design would have selected matched controls from the same standard metropolitan statistical areas as cases instead of the still current approach of a sample of convenience. Furthermore, whereas informants were required for cases, they were not required for the control subjects. Normative data from controls could be contaminated by unrecognized cases of very mild dementia. Very few controls, however, changed from CDR 0 to CDR 0.5, and their data can be examined separately. Urgency for brevity creates problems. Inquiry into medications is severely restricted, and a short, validated depression measure might have been preferable to the unevaluated depression items present. The neuropsychology battery is brief; nevertheless, alternative statistical approaches, such as item response theory, could have been used to select items to identify a broader range of disease status with less cultural bias. We had considered but never followed through on developing a neuropsychology profile that might have helped to distinguish patients with AD from patients with other dementing disorders. Overall, there was a strict focus on medical/psychiatric/neuropsychological aspects of AD; social and societal implications were largely ignored.

7. Main uses and findings

Review of publications that use the CERAD measures indicates that CERAD has had two major effects: (1) it has provided accepted standards for the clinical, neuropsychological, and neuropathologic diagnosis of AD, and (2) it has provided validated, normed measures that have been broadly used and that permit comparison across studies and settings. Tables 2 through 5 summarize the main studies in which the CERAD measures have been used. In addition, the neuropsychological battery in whole or in part continues to be used by the ADCs in their ongoing clinical and research studies (personal communication, K. Welsh-Bohmer, December 2006; J. C. Morris, December 2006).

The clinical, neuropsychology, and neuropathology batteries and the Behavior Rating Scale for Dementia have been used in major epidemiologic studies with diverse racial/ethnic groups (Table 2). Such uniform use in a number of different countries and within the same country with different population groups permits direct comparison of prevalence and incidence rates and facilitates assessment of alternative risk factors. By using uniformly operationalized diagnostic criteria and comparable assessment measures (we recognize that measures might need to be adapted to the cultural experience of those who are evaluated), any differences found are likely to be true differences or at least not artifacts of the assessment itself.

The clinical and neuropsychology batteries have also been used in clinical trials (Table 3), yielding information of national and international importance on the impact of hormone replacement therapy and, provided the study is funded, on the impact of selenium and vitamin E in preventing AD. We have not included drug trials carried out by pharmaceutical companies. Although we know that specific tests included in the CERAD neuropsychology battery have been used, we are not privy to the intervention being examined or to the findings. Such use is, however, an indication of the perceived value of these measures. Finally, some entrepreneurs have selected tests in the neuropsychology battery for on-line outreach, inviting persons concerned about their memory to be evaluated by telephone, with a potential diagnosis given in short order. Evaluation under medical supervision is also available. The appropriateness and impact of this approach have not been determined.

Table 4 lists the types of samples for which norms have been developed. They include clinic-based samples of diverse race/ethnicity in the U.S. and clinic-based norms for German-speaking countries. Norms have also been developed for internationally distributed community-based samples. The presence of such norms facilitates appropriate comparison; newly evaluated community residents can be compared with other community residents of comparable age, race/ethnicity, and education; patients at tertiary medical care centers can be compared with other patients at the same types of centers.

The CERAD neuropsychology battery (sometimes in whole, sometimes in part), has been used with various groups who, in addition to those listed in Tables 2 to 4, include Native Americans [53], older Israelis (in Hebrew) [54,55], elderly in Colombia [56,57], and older persons in India, China, Southeast Asia, Latin America and the Caribbean, and Africa [58,59].

The clinical battery has been referenced as a standard by several clinical studies that indicate that they used NINCDS/ADRDA and CERAD criteria for AD. In those instances, however, it is difficult to know whether the CERAD clinical battery or the CERAD clinical criteria were used. Compared with NINCDS/ADRDA, CERAD clinical criteria are stricter regarding duration of memory loss but more lenient regarding older age.

Table 5 shows the languages into which CERAD measures have been translated. The multiple translations (typi-

Table 2
Epidemiologic studies with CERAD batteries

Clinical Battery and Neuropsychology Battery used

Black/White Dementia Study: PIs: A. Heyman, G. G. Fillenbaum. Study based on participants of the Duke Established Populations for Epidemiologic Studies of the Elderly. Stratified random sample of 4,136 community residents (54% African American), age 65+ y, used to determine 3-year incidence of dementia; and 2-stage sample of those age 68+ y to determine prevalence of dementia [66].

Honolulu-Asia Aging Study (HAAS): PI: L. White. Survey of 3,734 community and institutional resident Japanese-American men age 71 to 83 y, 80% of the survivors of the Honolulu Heart Program [67].

Prevalence of Alzheimer's Disease in Provence (PREMAP): Random sample of 1,062 residents (community and institution) age 70+ y in southeastern France. Evaluation of persons with MMSE <24 by using CERAD batteries identified 177 cases of dementia (9.2%), including 82 cases of AD (5.5%). Prevalence of AD increased significantly with age and was higher among women (odds ratio, 4.24) and persons with no formal education (odds ratio, 2.47) [68].

Neuropsychology Battery only (entire battery, unless otherwise indicated)

Aging, Demographics, and Memory Study (ADAMS): PIs: R. Willis, B. Plassman. First nationally representative, population-based study in the U.S., designed to provide data on the antecedents, prevalence, outcomes, and costs of dementia and of "cognitive impairment, not demented". Sample of 856 participants in the Health and Retirement Study (age 70+ y) [69].

Cache County Study on Memory, Health and Aging: PIs: J. Breitner, K. Welsh-Bohmer. Continuing longitudinal study of 5,677 persons age 65+ y who were permanent residents of Cache County, Utah, to ascertain the prevalence and incidence of dementia and the development and impact of cognitive impairment [70–72].

Chicago Health and Aging Project (CHAP): PI: D. A. Evans. Longitudinal study of >6,000 residents (age 65+ y, 61% female, 62% African American, mean education 12 y), of three adjacent neighborhoods in Chicago. Data collection at ~3-year intervals; those who have reached age 65 since the previous interview date are then eligible to enroll, so maintaining the relevance of the sample [73].

Duke Twins Study: PIs: J. Breitner, B. Plassman. Ongoing study of intact pairs of veteran twins in the National Academy of Sciences—National Research Council Registry aged 62 to 73 y in 1990 to 1991, to ascertain concordance for AD in twins as a function of age and apolipoprotein E genotype [74,75].

Indianapolis-Ibadan Dementia Project: PIs: H. C. Hendrie, K. Hall. Sample of 2,494 Yoruba in Ibadan, Nigeria (age estimated from historic landmarks) and 2,318 community-resident and institutionalized African Americans in Indianapolis, Indiana, age 65+ y. Follow-up waves to identify incident dementia were conducted 2 and 5 y later and are ongoing [76,77].

Indo-US Cross-National Dementia Epidemiology Study: PI: M. Ganguli. Rural population (N = 5,126) age 50+ y, 73% illiterate, of Ballabgarh, Northern India. (CERAD neuropsychology measures adapted to the rural Indian experience [78])

Kame project: PIs: E. B.Larson, A. B.Graves (Borenstein). Survey of 1,985 community and institutional residents of King County, Washington, age 65+ y. Nearly all 100% Japanese heritage, the remainder with minimum of 50% Japanese heritage [79].

Korea: Stratified cluster sample of 706 people age 65+ y in Dong district of Gwangju, Korea, an urban area. (CERAD Word List tasks used to help identify presence of dementia.) [80].

Monongahela Valley Independent Elders Study (MoVIES): PI: M. Ganguli. Longitudinal study of a random sample (N = 1,350) of community residents age 65+ y (6th grade education, except for very elderly), in rural area outside Pittsburgh, PA [81].

Nun Study: PI: D. A. Snowdon. Longitudinal study of the School Sisters of Notre Dame (N = 678; age 75 to 102 y at entry). (Used selected CERAD neuropsychology measures.) [82,83]

Religious Orders Study: PI: D. A. Bennett. Nearly 1,000 older Catholic nuns, priests, or brothers (mean age 76 y, mean education 18 y, 32% male, 11% minority), volunteers from about 40 groups in 12 states and the District of Columbia, who agreed to annual clinical evaluation and brain donation. (Used selected CERAD neuropsychology measures.) [84]

Rush Memory and Aging Project: PI: D. A. Bennett. More than 1,000 volunteers, mean age 81 y, 8% minority, 28% male, mean education 14 y (but a third had <12 y of education), drawn from a variety of living arrangements, who agreed to detailed, repeated assessments and donation of neurologic material and muscle at death. (Used selected CERAD neuropsychology measures.) [85]

Taiwan: Two-phase study of a stratified random sample of 2,915 inhabitants age 65+ y in southern Taiwan. After initial screening, subjects were administered CERAD Neuropsychological Battery and neurobehavioral examination [86].

Veterans Study of Memory in Aging: PI: B. Plassman. Carefully selected group of World War II Navy and Marine veterans hospitalized during military service with head injury, and controls. Complete information on 548 with and 1228 without head injury, used to ascertain risk for dementia as a function of head injury and apolipoprotein E status [87].

Neuropathology battery

A review of population-based studies indicates that the CERAD Neuropathology Protocol appears to be the generally used standard [52].

CERAD Neuropathology Protocol has been adopted by the College of American Pathologists for practice guidelines on autopsy pathology [44].

The CERAD Neuropathology Protocol is the foundation for recommended diagnostic protocol for dementia with Lewy bodies [45].

BrainNet Europe Consortium: Comparison of interlaboratory rating reliability based on the CERAD, Braak and Braak, and NIA–Reagan Institute neuropathologic criteria [88].

Oxford Project to Investigate Memory and Aging (OPTIMA): Study in which by 1997, 200 patients with cognitive impairment or dementia had been referred by their physicians, and by 2002, 158 cognitively intact community residents age 60 to 91 y had enrolled. CERAD neuropathologic (and other criteria) were used [89].

Religious Orders Study: PI: D. A. Bennett. (Used CERAD, NIA-Reagan, and Braak criteria.) [84]

U.K. Medical Research Council Cognitive Function and Ageing Study (MRC CFAS): Neuropathology data come from decedents who participated in a longitudinal study of stratified random samples of residents age 65+ y (>18,000 individuals) selected from 6 centers (including urban and rural areas) in the UK [90].

Behavior Rating Scale for Dementia

Alzheimer Disease Cooperative Study: representative studies: To examine emergence of behavioral pathology [91]. Included, among other measures, to assess behavioral pathology [92]. Included in the Alzheimer's Disease Cooperative Study (ADCS) Instrument Development Project [93].

Taiwan: survey of the prevalence of dementia. Both the CERAD neuropsychology battery and the Behavior Rating Scale for Dementia were used in this survey [86].

Abbreviations: PI, principal investigator; MMSE, Mini-Mental State Examination.

cally done in the conventionally approved manner with back translation) facilitate testing of patients within countries such as the U.S. and Canada that have a multilingual population, as well as facilitating cross-national comparisons. We have not included English as spoken in Australia in this table, but we would mention that even when ostensibly the same language is spoken in two different locations, it might be important to evaluate the measure in each location if there are indications that terms are differently understood in the different locations or might be understood differently by different residents of the same location. To make sure that the measures remain acceptable (and hopefully equivalent),

Table 3
Major clinical trials that have used CERAD materials

The Women's Health Initiative Memory Study (WHIMS): a randomized, double-blind, placebo-controlled clinical trial of 4,532 (92.6%) of the 4,894 postmenopausal women free of probable dementia, aged 65 y or older, who were enrolled in the Women's Health Initiative (WHI) estrogen plus progestin trial in May 1996. Participants received either 1 daily tablet of 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate (n = 2,229) or a matching placebo (n = 2,303). Incidence of probable dementia (primary outcome) and mild cognitive impairment (secondary outcome) were identified through a structured clinical assessment [94–97].
Prevention of Alzheimer's Disease by Vitamin E and Selenium (PREADVISE): add-on study to Selenium and Vitamin E Prostate Cancer Prevention Trial (SELECT) (LMTS). PREADVISE has enrolled >5,200 men (18% minority; age 62+ y if white, age 60+ y if African American or Hispanic), all of whom are participants in the SELECT trial, running in over 400 clinics. All are administered a brief cognitive screen, developed from the measures of the CERAD neuropsychological battery and the CERAD database, with additional assessment if warranted [98,99].
Research into Memory, Brain function and Estrogen Replacement (REMEMBER): pilot study, based on a random sample of 428 women age 60+ y in Adelaide, performed before initiation of major study. Used CERAD word list, category fluency (Animals), and 15-item Boston Naming Test [100].

item order has sometimes been changed (eg, for the Behavior Rating Scale for Dementia in Arabic), items have been substituted (eg, in the abbreviated Boston Naming task used in Finland), and different words have been used (eg, in the "American" vs "European" Spanish translations of the Word List).

8. Current status of CERAD

At the end of the first 10 years, CERAD had developed standardized versions of the basic assessments needed to evaluate AD. They were being used in the memory disorders clinics of major tertiary care medical centers nationwide and in translation in clinical centers in Brazil, French-speaking Canada, France, Italy, Portugal, and Spain. The CERAD measures had also been adopted for use in major national and international epidemiologic surveys. Hitherto, each epidemiologic study of dementia in the U.S. had used its own assessments, creating disbelief in findings [15].

Continued funding depended on competitive renewal through National Institutes of Health's standard research funding mechanism. This mechanism is designed well for evaluating hypothesis-driven research, but CERAD's mandate was not to develop or test hypotheses. The name itself was misleading, because CERAD was not a registry as that term might generally be understood [60,61]. CERAD's mandate was to produce measures that would facilitate hypothesis-driven research. A pedestrian but crucial requirement for scientific communication is the existence of commonality of terms and standardization of definitions. CERAD filled this requirement and was prepared to do more. Such activities, however, are rarely recognized as fundable under a research aegis.

As investigation into AD progressed, it had become increasingly clear that there were subtypes of AD that might, in fact, be distinct dementias that demanded unique diagnostic procedures and interventions (eg, frontotemporal

Table 4
Norms: representative selection

Clinic-based data (representative references)
United States:
White (CERAD data) [101,102], white (ADC clinic, age 85+ y) [103]
African American (CERAD data) [38,104]
White and Native American [53]
Spanish-speaking [105]
German-speaking countries: clinics can compare their information on patients with community-based norms by going to www.memoryclinic.ch and following the directions there (a performance profile and z-scores are provided; site developed by A. H. Monsch)
Community-based, including epidemiologic studies
Australia: sample: healthy elderly, n = 243 [106]
Brazil: CERAD Neuropsychological Battery administered to 85 normal controls, 31 AD patients at CDR 1, and 12 AD patients at CDR 2. Performance of controls was similar to that of a U.S. control sample [107]
Finland: In a sample of 40 cognitively normal individuals age 58 to 85 y, education effects, but no age effects, were found [108]. Comparison of 15 cognitively normal, 15 amnestic MCI cases, and 15 mild probable AD cases [109].
Jamaica: Norms and ability to discriminate between normal and demented persons, based on 72 cognitively normal people and 12 people with dementia age 65+ y [110]
Korea: 618 healthy, cognitively normal volunteers. Norms provided for four overlapping age groups (60–74, 65–79, 70–84, 75–90 y), three levels of education (0–3 y, 4–6 y, 7+ y), and by gender [111]
Nigeria (Yoruba): 100 normal, healthy adults age 65+ y [112]
Switzerland: Norms based on 617 participants in Basel Study on the Elderly (Project BASEL), 185 women, 432 men, age 53–92 y [113]
United Kingdom (African-Caribbean): African Caribbean residents (n = 285, age 55–75 y) of south London, UK. CERAD measures: Verbal Fluency (animals), Boston Naming, Word List [114]
United States: White (from Black/White Dementia Study and MoVIES study) [38,81]; African American (from Black/White Dementia Study and African Americans in Indianapolis) [38,115]; Japanese heritage (from Kame Project and HAAS study) [116,117]

Table 5
Languages into which CERAD measures have been translated

Language	Clinical battery	Neuropsychological battery	Behavior Rating Scale for Dementia	Individual measures only
Arabic			+	
Bulgarian	+	+		
Chinese		+	+	
Estonian		+		
French	+	+	+	
Finnish		+		
German		+		
Hebrew		+	Forthcoming	
Italian	+	+		
Japanese	+	+	+	
Korean		+		
Norwegian		+		
Portuguese		+		
Russian		Planned		
Spanish	+	+		
Swedish				Word List
Swedish for Finland		+		

dementia, Lewy body disease). In addition, other dementing disorders were well-known. CERAD had begun to develop diagnostic criteria and was reviewing appropriate neuropsychological measures to assess these conditions. Completion of this task, in an environment that required no new start-up, could have facilitated identification and comparison of these conditions.

At the time that funding ceased, CERAD was developing measures to assess important end points for end-stage disease, service use and need throughout the course of the illness, and a brief assessment for use in primary care. Importantly, CERAD had a particular interest in potential dementia prodrome, a term coined to describe a very early phase in the dementing process, possibly a logical progression between normal cognition and dementia, particularly AD [62,63]. CERAD had already selected clinical and neuropsychological assessments that seemed appropriate and developed diagnostic criteria. Enrollment of such cases and their eventual brain autopsy could have furthered knowledge of the association (or lack of association) between clinical and neuropathologic manifestation across the entire range of cognition. This has become recognized as an increasingly important area, in which significant problems persist because of multiple diagnostic criteria and diversity in assessments.

Further development of the CERAD neuropathology protocol also ceased. As a consequence, the Neuropathology Task Force was unable to modify the battery to more appropriately reflect changes seen with other dementias (eg, vascular dementia, frontotemporal dementias, and dementia with Lewy bodies) and to incorporate the use of appropriate markers, eg, alpha-synuclein immunohistochemistry. Although the CERAD neuropathology protocol has become the standard for neuropathologic assessment in epidemiologic studies [52], the lack of ability to update the protocol has reduced the ability to aggregate standardized data from multiple centers, mitigating the ability to glean important correlative and other information.

Careful consideration of funding for activities basic to sound research but not necessarily addressing specific research topics (eg, development of valid, reliable, and acceptable measures; new statistical approaches) is critical to sound, generalizable, research findings.

9. CERAD's legacy

By the end of its first decade (1996/1997), seven CERAD-based theses or dissertations had been accepted, more than 50 articles by CERAD investigators had been published or were in press, and achievements were summarized in a supplement to *Neurology* [64]. Now, 10 years later, approximately 400 articles have been published. Figure 1 shows the number of articles published, and Figure 2 shows the number of citations for 1992 to 2006. The vast majority have appeared in the fields of medicine and neuroscience, with substantial representation in psychology. CERAD has also made its way in genetics, the health professions, and pharmacology. According to the SCOPUS database (searched on "cerad" or "consortium to establish a registry for Alzheimer's disease"), CERAD-related articles have appeared in 117 different journals involving 147 different authors.

CERAD and its legacy live on. We are pleased to see that through the National Alzheimer Coordinating Center (NACC), ADCs are now strongly encouraged to use the set of carefully evaluated, predetermined measures selected for the Uniform Data Set [65]. The CERAD materials remain in demand. The de-identified database has been archived with NACC. It is also available directly from the CERAD central office to users who can show that they are familiar with AD and intend to use the data in a responsible manner—conditions placed on access by the participating sites. Informa-

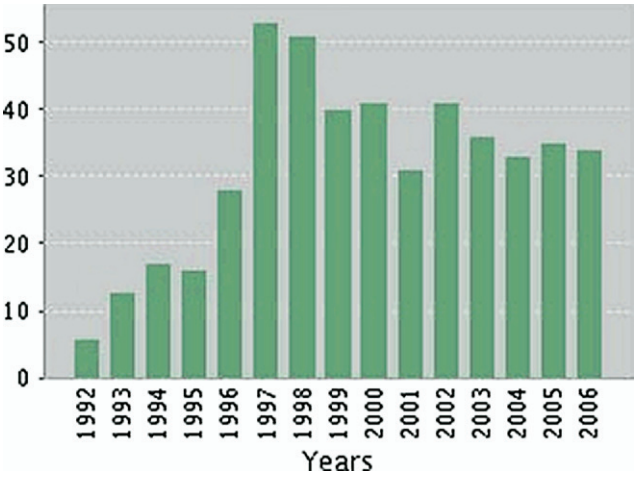

Fig 1. CERAD publications 1992 to 2006.

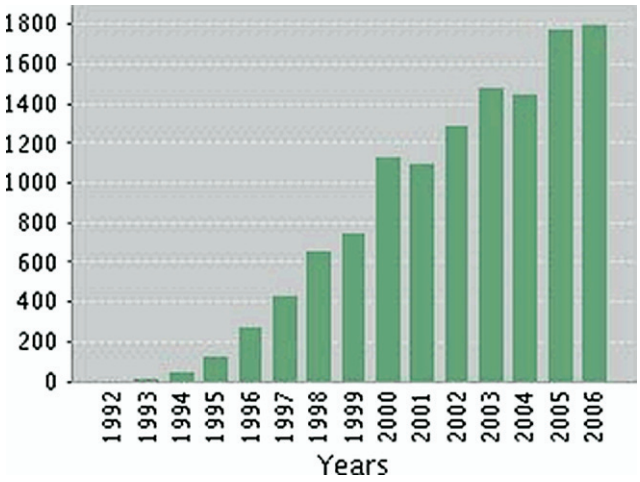

Fig 2. Citations to CERAD 1992 to 2006

tion on CERAD is available through the CERAD website, http://cerad.mc.duke.edu, and from the contacts listed there.

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