Towards a program of cross-cultural research on the epidemiology of Alzheimer's disease

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Cross-cultural and international comparisons may illuminate how Alzheimer's disease and other major dementing illnesses are influenced by environmental, cultural, societal, and genetic factors. The meaning and value of such comparisons depends upon the care with which the studies are conducted, the use of cross-nationally standardized methods and criteria, and a great sensitivity to how culture, language, and education determine illness recognition, diagnosis, migration, and survival.

EPIDEMIOLOGIC research often serves two simultaneous purposes: as a research tool for examining biological, pathologic, and medical processes in populations, and as an aid to medical and public health practice, administration and planning. Efforts to accurately assess patterns of occurrence of Alzheimer's disease and vascular dementia in defined community and national populations address both purposes. Cross-national comparisons have limited administrative utility, but provide a special opportunity to identify factors influencing the development of dementia that may be inapparent within a more homogeneous population.

The 'graying' of the world is leading to dramatic increases in the burden of dementia and other age-dependent disabling conditions in almost every nation. If the coming avalanche of demented elderly is not somehow avoided, the likely result will be an overloading of health care systems throughout the world. Effective means for preventing, reversing, arresting, delaying, or ameliorating the most common types of dementia (Alzheimer's disease (AD) and cerebrovascular dementia (CvDem)) must be developed.

The main focus of this review will be on concepts and methods as related to comparative cross-cultural and international epidemiologic research on rates, clinical course, and risk factors for AD and CvDem. For more specific, detailed epidemiologic information several reviews have been published in recent years[1-5]. The second half of this review is specifically intended for researchers designing or contemplating clinical or epidemiologic research projects on dementia, and special attention is given to several practical issues and difficult methodologic problems they must address.

RATES: Definitions of prevalence and incidence

Prevalence is simply the proportion of people in a defined group (as all residents of a city) who have a disease or characteristic, in this case, dementia. In contrast, an incidence rate is the number of new cases that develop in a defined group (among those who do not already have the condition) during a specified time interval, typically one year. In the case of dementia, prevalence rates provide the most important indicator of how many citizens of a city or nation are impaired and in need of care because of dementia. The incidence of dementia is much more difficult and costly to measure but is most important to questions of pathogenesis and causation since it is the population measure that best represents risk for the development of dementia.

When we wish to compare rates of dementia across populations, or in different subgroups, we must take into account the age distributions of those different populations or subgroups so that we can disentangle differences due simply to the age make-up from differences more directly related to health. This is particularly important for dementia because rates increase exponentially with advancing age. While the numerical value of rates can be statistically adjusted to remove most of the effects of demographic differences among populations, it is often easier and more meaningful to compare age-specific rates. Age-specific prevalence and age-specific incidence rates are commonly presented for five-year age groups, i.e. 60–64, 65–69, 70–74, etc. Plotting age-specific prevalence and incidence rates allows for the estimation of a baseline (intercept) rate (perhaps at age 50 or 60 years), and a slope of increase in the rate with advancing age. In comparing patterns of occurrence of dementia in different groups we need to be able to distinguish differences due to baseline level from those that are associated with differences in slope of the age-specific rate, since the two alternatives imply different pathogenic processes.

Relationships between prevalence, incidence, duration, residence, and migration

Incidence rates for dementia tend to be substantially lower than prevalence rates. This reflects the fact that the average demented person lives a few years after the dementia first becomes apparent. Because usual survival exceeds one year, cases accumulate. Most of the cases of dementia one finds in community populations had their onsets 2–12 years earlier.

Prevalence rates may also be influenced by migration patterns. Dementia often leads to a change in residence. If the cognitively impaired person needs assistance or supervision, he or she may move to live with a friend or family member. The influence of dementia on residence and migration patterns will be determined by sex, socioeconomic factors, religion, culture, available community resources for health care, local community housing situations, and other factors. In many societies, elderly men can stay in their homes when they become disabled or demented because most have a wife who will care for them. Most elderly women are widows. If disabled, someone must come to live with them or they must go to live with someone else. Taking care of a demented mother or step-mother may be much more burdensome for a family living in a city such as Tokyo–where homes are small and both husband and wife must work–as compared with a more rural area. Such socioeconomic forces must be considered in interpreting demographic and epidemiologic data, as well as in planning where (in what community) and how to measure the prevalence and/or incidence of dementia so that results will be interpretable and comparable with those of other surveys.

Published prevalence estimates for defined populations

When an effort has been made to identify cases, dementia has been found among older persons in all or nearly all populations. In virtually every such study, the most important causes have been AD and CvDem. Estimates of the prevalence of dementia have been reported from population surveys done in the US, several European countries, and several Asian nations[1,6–15]. Among citizens aged 65 and older, most estimates of the prevalence of all-cause dementia of at least moderate severity have been in the range of 3–10%. In general, estimated rates from the Asian nations have been somewhat lower than from the US, England, and Europe. For most European and American populations, prevalence rates for AD have been approximately half the total dementia figures, while rates for CvDem have varied between 0 and 30% of the total dementia prevalence values. These relationships tend to hold at all ages. In most surveys from Japan, China, and Taiwan the relative frequencies are reversed, with rates of CvDem being 30–60% of the values for total dementia, and rates of AD being 20–40% of the total dementia prevalence rates.

In a valuable review of reported surveys of dementia, Jorm *et al.*[1] noted that although age-specific prevalence rates of dementia (all cause) varied widely, a fairly uniform pattern emerged when they were viewed collectively[1]. The variation in reported prevalence estimates among nations are mostly in a range that might be explained by methodological difference in case detection and classification. The most consistent finding across nations and among research studies was an increase in rates of dementia with advancing age, age-specific prevalence rates doubling about every five years. A worldwide average age-specific prevalence curve can be approximated by a trajectory that begins at about 1% at age 60, then rises to 2% at 70, 4% at 75, 8% at 80, and 16% at age 85 years. These rates are for dementia of all causes and of at least moderate severity.

AD:CvDem ratios

Since AD and CvDem are believed to occur as a result of distinct and independent pathological processes, differences in the ratio of their rates would be expected to reflect true differences in the rates of one or both conditions. Although social, cultural, and methodologic factors certainly affect the detection of cases of dementia, most experts expect these factors to apply equally to all causes of dementia, i.e. sensitivity for the identification of demented persons would be expected to vary substantially across studies, but to be similar for AD and CvDem within a study population. Thus, if the AD:CvDem ratio differs between two populations, it gives credence to the idea that the difference is related to something biological, rather than to methods of detection.

If one compares averages of dementia rates and AD:CvDem ratios from Japan with similarly computed average figures from the US and Europe, it appears that prevalence rates for AD in the US and Europe are 2–3 times those in Japan, while the CvDem prevalence rate in Japan is 1.5–2 times those for the US and Europe[8–10]. These calculations assume equal sensitivities for the detection of dementia. There is some suspicion, however, that the sensitivity of case detection might be lower in Japan, because of some aspects in the early steps of case finding in the Japanese surveys, and because published prevalence estimates for Japan are lower than recent prevalence estimates for US and European populations. If the overall sensitivity of case detection methods in Japan were half the sensitivity of

detection methods used for American surveys it would explain the observed lower rates of AD, but the excess of CvDem would become even greater. A higher prevalence of CvDem could be due either to a higher incidence of vascular dementia in Japan (a hypothesis fairly consistent with known high rates of non-lethal stroke relative to the US), or to a greater duration of survival of persons with vascular dementia in Japan, perhaps because of differences in the proportions of subtypes of stroke and vascular dementia. A lower prevalence of AD in Japan could be due to either a shorter survival, or a lower incidence rate. A lower incidence of AD could be mediated by differences in environmental or life style determinants, or a lower prevalence of familial predisposition of AD. These considerations have led to a great interest in research into these issues, since new and important knowledge concerning the pathogenesis of AD or CvDem or both is likely to result.

Although a difference between Asian and European ancestry populations in the AD.CvDem ratio is best documented for Japan, similar findings have been reported from China[16] and Taiwan[17,18]. However, in a recent survey carried out in Shanghai using methods similar to those of most American surveys, the ratio and rates of AD and CvDem were similar to those that have been found in European-ancestry populations[15]. On the other hand, a study of Chinese–American demented residents of a nursing home in New York city supported a low AD:CvDem ratio[19].

Incidence

In most studies, the annual incidence of dementia tends to be one-quarter to one-fifth the prevalence[16,20,21]. Although there have been few data sets large enough to allow confident estimates, the age-specific dementia incidence curves that have been published tend to parallel the prevalence curves. Roughly similar AD:CvDem ratios have been found in prevalence and incidence studies, a finding not supporting major differences in duration of survival between AD and CvDem.

Clinical course and survival

The clinical courses of AD and CvDem are part of the definitions of the two diseases. AD has an insidious onset and progressive course. As currently envisioned, patients never recover from AD, and improvements, when they occur, are temporary. For a secure diagnosis of AD, many researchers require not only a history of decline over a period of at least 6–12 months, but insist on confirmation of the diagnosis by autopsy or by observing the clinical course over an additional two years. During that interval, the condition worsens at least slightly, and no other apparent cause for the cognitive impairment becomes apparent. If a stroke occurs it may be taken as evidence of pre-existing cerebrovascular disease, and (depending upon neuroimaging and other factors) may serve to shift the diagnosis from 'pure' AD to mixed AD/CvDem.

Prospective studies of the clinical courses have shown that individual AD cases are quite varied in their rates of decline in cognitive functioning, and in the spectrum of other signs and symptoms of the disease[22–24]. A substantial proportion of AD patients show only modest declines in cognitive functioning during a two year follow-up, with or without progression of behavioral changes (wandering, delusions, socially inappropriate behaviors, etc.), motor abnormalities (in extrapyramidal functioning and ability to carry out sequential or rapid alternating movements), or capacity for independent functioning. Neither age of onset, sex, nor clinical characteristics at the time of diagnosis are reliable predictors of the rate and quality of the subsequent clinical course. The exception to this is found in cases of early onset autosomal dominantly inherited familial AD, in whom the disease tends to progress more precipitously[25]. The more common type of familial AD is characterized by a history of dementia in an occasional first-degree relative and is not distinguishable from sporadic AD in age of onset, clinical features, or clinical course[26].

Although survival has been reported to be shorter in persons with CvDem than in AD, this has not been a consistent finding[27,28]. It now appears that AD has a moderate adverse effect on survival, increasing the risk of dying in the next year by 1.5–2 times and decreasing the sex-and age-specific life expectancy by 30–50%. When death occurs, it is usually attributed to the same causes as in non-demented persons, and usually occurs before the dementia has become profound. Profoundly or severely demented persons are clearly at increased risk for injuries (falls and fractures), aspiration pneumonia, and infections associated with pressure sores, pneumonia, and/or urinary tract infections.

AD: risk factors and etiology

Case-control studies of AD have illuminated the great importance of advancing age, the existence of familial predisposition, and an association of head trauma with the subsequent development of dementia[29–31]. Although a number of other factors have been implicated, none have been consistently found in the majority of the published reports.

It is clear that AD risk is commonly influenced by familial or genetic factors. A familial predisposition may be important in a substantial proportion (perhaps half) of the cases of AD in some populations[32]. It is

presumably dependent upon multifactorial inheritance and/or genetic factors with variable penetrance, since no specific Mendelian inheritance pattern has been discerned. These cases appear clinically indistinguishable from the true sporadic cases. There is also a rare, autosomal dominant pattern of inheritance, several kindreds of which have now been studied. It appears that this form of the disease is genetically heterogeneous, genetic linkage studies having located the gene at different sites in different kindreds[33-36]. Studies of twins suggest that environmental determinants of the development of AD are of great importance, since even monozygous twins are commonly discordant for the disease, whether or not there is a history of AD in other first degree relatives[37].

Other indications of the importance of genetic factors come from studies of patients with Down's syndrome (DS), in whom the neuropathological manifestations of AD are nearly always noted at autopsy by age 30–40 years[38,39]. Two other related observations bear on this mysterious relationship: (1) DS occurs more often among first degree relatives of AD cases than among the relatives of control[37], and (2) some (but not all) researchers have noted that mothers of AD patients were significantly older at the birth of the AD case than were the mothers of non-demented persons[41,42]. To add even further fascination to the puzzle, the gene coding for the main protein constituent of a hallmark neuropathologic lesion of AD (the beta amyloid protein for neuritic amyloid plaques) is located on chromosome 21, not too far from the area of that chromosome that must be triplicated for the Down phenotype to be expressed[43].

Case-control studies and research on professional boxers support a role for head trauma in the later development of AD[44,45]. However, it seems likely that this factor is important in only a subset of AD cases, since a history of head trauma is elicited for a relatively small proportion of cases of dementia. Two possible mechanisms by which trauma might act are: (1) transitory disruption of the blood-brain barrier, possibly leading to immunologic abnormalities, or (2) reduction in neural reserves (fewer neurons and/or a reduction in synaptic connectivity), thereby lowering the threshold at which age- or Alzheimer-related processes might lead to clinically significant impairments of cognition and behavior.

Recent studies have implicated low education as a risk factor for AD[16,46-49]. Until just a few years ago most authorities believed that education and socioeconomic status had little influence on the development of dementia. While it was recognized that a higher proportion of older persons with few years of schooling received poor scores on nearly all tests of cognitive functioning than did more highly educated persons, it was believed that true dementing illnesses were equally prevalent across levels of educational attainment[50]. In fact, anecdotal knowledge of cases of dementia among highly educated, socially prominent people led many to speculate that dementia might be more obvious, and therefore might be recognized more commonly, in persons whose premorbid functioning was at such a high level that even minor declines would bring them to medical attention. As mentioned, recent analyses have suggested the opposite—that a less educated person may be more likely to develop AD, and that the disease may progress more rapidly in less educated persons. Three mechanisms that might be involved are: (1) persons with fewer neuronal and synaptic reserves may be less likely to be selected to receive further education, (2) persons with low education, because their brains are less intellectually exercised, may have fewer neuronal and synaptic reserves as a result of suboptimal maintenance, repair, and adaptation mechanisms, or (3) lifelong low socioeconomic status and associated occupational exposures of persons with few years of education might be associated with more accumulated injury and brain cell loss. These issues and questions are currently a focus of major research interest.

A role for aluminum in the development of AD is most powerfully supported by the observation of high levels of that element in the paired helical filaments seen on electron microscopy in the neurons of AD patients[51]. Although occasional reports continue to support the possibility of an etiologic role for aluminum[52-54], the bulk of available evidence seems to suggest that aluminum deposition may be more appropriately viewed as a consequence than a cause of the pathogenic mechanisms involved in AD.

Although it is quite clear that there are more women with AD than men, sex is at most a weak risk factor for the development of AD. In many nations, older women not only outnumber older men, they also seem to come to medical attention more often than do men. In the case of dementia this may reflect a situation in which older men are more likely to have a spouse to care for them than are older women. In many cultures, older women are not only expected to care for themselves, but are also expected to perform more domestic functions than older men. Longer survival after the development of disease, due to a generally greater life expectancy, may also contribute to the reported higher age-specific prevalence of AD in women. Although the majority of prevalence studies show an association of AD with female sex, incidence rates tend to support similar risks among men and women[16,21,29].

There have not yet been adequate studies in populations with sufficient ethnic diversity to address the role of race and ethnicity, or with methods that would allow for confident comparisons with studies in other populations. Although there are certainly major differences in reported rates of AD from different nations, these could as well be due to methodologic differences as to biologic

differences. Further, if cross-national differences in risk are found, it will not be immediately apparent if they are attributable to genetic or to environmental differences. Nonetheless, there has been tantalizing anecdotal information suggesting the possibility of very low rates of AD in Nigeria and in American Indians. As mentioned above, AD.CvDem ratios also suggest the possibility that persons of Japanese or Chinese ancestry may also have low rates of AD compared with European-ancestry persons. In recent years it has been widely recognized that investigations aimed at defining the risk for AD in persons of different or similar genetic constitution living in different or similar environments might provide information of great value to our efforts to understand the pathogenesis of the disease.

CvDem: risk factors and etiology

Factors that determine which persons with cerebrovascular disease become demented are currently viewed as reflecting the location and extent of infarcted brain tissue, rather than mechanism-specific factors. Ischemia in the absence of infarction is not thought by most authorities to be involved in dementia. Although certain types of stroke may be more likely to lead to dementia than others, prevention of cerebrovascular dementia has generally been thought of as part of the problem of preventing strokes. Future strategies for the prevention of CvDem may benefit from epidemiologic research aimed at more specific vasculopathic mechanisms. Comparative cross-national epidemiologic research investigations may provide special insight into these questions, since rates of subtypes of cerebrovascular disease may vary substantially across nations and cultures.

Methodologic aspects of cross-national epidemiologic research

Sources of data: case finding for epidemiologic research

For most diseases, prevalence and incidence rates are based on data supplied by hospitals, clinics, physicians, or other health care providers. If one depends upon such sources for dementia, observed rates are certain to be both biased (by sex, socioeconomic stratum, etc.) and to greatly underestimate the true occurrence of dementia. Cross-national comparisons based on such data would be essentially meaningless. The reasons for this are that clinical diagnoses tend to be made in an unstandardized way, and many (usually most) cases of dementia in the community are not diagnosed or even identified as having cognitive impairment.

To identify cases and estimate true rates in a defined population, a carefully designed survey, including individual testing of each person, is essential. If the population is too large for all to be examined, a sample must be examined. In order to establish the diagnosis of dementia, persons who might be demented must receive an objective evaluation of their cognitive functioning and neurological status, some sort of evaluation of their general health and medical history, and a separate history must be obtained from a family member, close friend, or other reliable sources. Confirmation of the diagnosis often requires further observation of the clinical course, or autopsy. The identification and classification of cases of dementia in a community survey require the use of appropriate instruments, methods, and criteria, and extremely rigorous attention to standardization and quality control at every step.

Diagnostic criteria and definitions

Advanced, textbook-typical cases of dementia are easily recognized and diagnoses are usually straightforward. In large part as a result of community studies, it has become apparent that most cases of dementia are neither textbook-typical nor easily diagnosed. There is a subtle gradient from the usual changes in behavior and cognitive functioning that occur with aging, through the changes of early or mild dementia, progressing to moderate and severe dementia. Alzheimer's disease typically has an insidious onset and there are no reliable sentinel events to mark when severity levels are attained. The onset is often so gradual that family members do not recognize that anything is wrong until the cognitive impairment is quite marked, or until socially disruptive, abnormal behaviors become inescapably apparent. Recognition of these depends heavily on the nature of the person's previous cognitive and behavioral functioning, and upon relationships with other family members. The common failure of family members to recognize the development of cognitive impairment in an aging spouse or parent may require heavy reliance upon cross-sectional measures of level and quality of cognitive functioning and behavior. Taking into account what is known of educational attainment, social functioning, and occupational complexity during adult life, the examiner must consider the person's performance on testing and his current level of functioning with relation to an imputed level of functioning at a prior time. From these data and informed guesses, the examiner makes judgements regarding the existence, extent, and quality of cognitive impairment and deterioration that might have occurred.

Great progress has been made in the standardization of diagnoses of dementia in recent years. At present the

most widely accepted criteria for dementia (all-cause) and AD are from the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised (DSM-III-R)[55]. The tenth revision of the *International Classification of Diseases*, although not yet available, will include improved definitions of dementia (all cause), AD and CvDem. In addition, slightly different research criteria have been recommended for AD (NINCDS-ADRDA research criteria[56]) and for CvDem (the California criteria[57] and the NINCDS AIREN criteria[58]). Although these represent major improvements, there is no single, globally accepted set of definitions and criteria. Even with the DSM-III-R criteria, actual application remains problematic, since substantial interpretations and semi-arbitrary clinical judgements must be made in applying these criteria to individual subjects in heterogeneous populations and across groups that vary in culture, language, education, and occupation.

While most medical centers focus their diagnostic efforts on differentiating among possible causes of dementia (AD, CvDem, etc.) in persons with recognized dementia, it is often more difficult in community surveys to determine if dementia is or is not present, and to assess its severity. DSM-III-R criteria for dementia include five elements (individual criteria), three of which involve impairments in cognitive functioning. The first criterion requires *demonstrable evidence of impairment in short- and long-term memory*, and implies that the demonstration of such impairment should be accomplished during the course of an examination. The second criterion extends this requirement to include *at least one other cognitive abnormality* (in addition to the memory problems), such as an impairment in abstract thinking, judgement, language or other higher cortical function, or personality.

The third criterion reflects severity and the impact of the cognitive impairments on daily life – it requires that these *disturbances interfere 'significantly ··· with work or usual social activity'*. This criterion represents a *de facto* assessment of severity. The evidence that such interference exists should come from independent observations or reports on the individual's behavior; more is required than simply a clinical judgement that the level and quality of cognitive impairment (based on interview and test performance) are sufficiently severe so that they must interfere with work, social, or other daily life activities. Although it is sometimes reasonable to accept the patient's own descriptions, one would not generally wish to rely entirely on the demented person as a credible historian for himself. Usually the only information addressing these questions will be obtained from one or more proxy informants: a spouse, child, or other family member. Their expectations as to what comprises usual activities and relationships are likely to be strongly influenced by cultural factors, their relationship to the subject (a spouse may have different expectations than a child), and personal characteristics of both the subject and the informant (sex, age, education, etc.). This criterion is very difficult to apply equally across national populations as well as among groups within nations.

The fourth and fifth DSM-III-R criteria for dementia are intended to identify cases of cognitive impairment for which other causes are likely, including delirium and obvious organic disease.

Diagnostic criteria for AD

In order to meet DSM-III-R criteria for AD, the patient must meet criteria DSM-III-R for dementia, onset must be insidious and the clinical course must be one of progressive deteriorations, and no other likely cause must be apparent. For research purposes, the NINCDS-ADRDA criteria are often used. According to these criteria, the diagnosis can only be considered definite when neuropathologic confirmation is available (usually by autopsy). In order to meet NINCDS-ADRDA criteria for *probable AD* the following are required: (1) the diagnosis of dementia must be established by clinical examination (including mental status testing) and neuropsychological evaluation, (2) deficits in memory must be sufficient to interfere with everyday activities relative to past performance, (3) deficits must be documented in one or more other cognitive domains, (4) a history of onset between age 40 and 90 years with progression over a period of at least one year is required, (5) there can be no disturbance of consciousness (as delirium, coma) and (6) no other disorders or brain diseases can be present that could account for the deficits in cognition and memory. The NINCDS-ADRDA criteria for *possible AD* correspond generally to those for probable AD, except that other brain disorders (such as cerebrovascular disease of Parkinsonism) may be present if they are not thought to be the cause of the cognitive impairment, *or* the cognitive deficit is limited to a single cognitive domain.

Diagnostic criteria for CvDem

Although there are DSM-III-R criteria for CvDem, they are somewhat less satisfactory than those for AD. Diagnostic criteria are currently being developed by an international committee of experts convened by the National Institute of Neurological Diseases and Stroke (NINDS), but are not yet published (at writing)[59]. At present, the criteria most useful for research purposes are for 'ischemic vascular dementia' (IVD), developed by the state of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC IVD criteria)[58]. These criteria widen the vascular disease concept somewhat,

emphasize neuropathologic confirmation, include the results of neuroimaging in the information to be considered in classification, and address issues related to disease subtypes and certainty of diagnosis. The older systems used for diagnosing CvDem tended to rely upon a history of one or more prior strokes, with a causally reasonable temporal relationship to the impairments in cognitive functioning, other evidence of cerebrovascular disease (as focal signs), and a history of sudden onset and stepwise progression. The Hachinski score, an index integrating information on cardiovascular risk factor status, clinical manifestations, and history of hypertension, sudden onset and stepwise progression, has also been used by many clinicians and researchers as a measure of the likelihood that a dementia syndrome is associated with cerebrovascular causes[59].

These diagnostic criteria are time consuming and awkward to apply; why are they needed?

Progress in understanding the causes, pathogenesis, and clinical course of the major dementing illnesses has been unimpressive, compared with other major diseases targeted by the medical research community. Comparisons between studies conducted by different research teams at different sites, especially between nations, have often led to concern that cases were not being similarly categorized. These considerations lead some to wonder if our slow research progress might not be related to variability and imprecision in classification; perhaps we have been working with groups of cases that are both pathogenically heterogeneous and variable across research studies. These concerns appear to be substantiated by a poor correlation described by several researchers between antemortem and postmortem diagnoses (see misclassification, below). In the absence of knowledge that would allow classification according to cause, it seems necessary to require that researchers utilize a rigorous system for classification according to clinical manifestations.

Severity

Many researchers believe that the natural history of dementia usually includes a prolonged interval when the condition is mild, a somewhat shorter period of moderate impairment, and a shorter interval during which the cognitive impairment is severe. The implication of this is that most cases of dementia are mild, fewer are moderate, and an even smaller number are severely impaired. Although this gradient of frequency by severity has not always been observed, and survival and clinical course are not reliably predicted on the basis of a cross-sectional assessment of severity, the concepts are generally accepted. A closely related, particularly troublesome, aspect of research on dementia is that there is no clear qualitative or quantitative demarcation between mild dementia and normal aging or low-normal cognitive functioning. All of the usual measures used to define the severity of dementia become indistinct at the borderline between mild dementia and the mild deteriorations in cognitive and behavioral functioning that most accept as part of normal aging.

The meaning of 'severity of dementia' is somewhat ambiguous. From the clinician's point of view, severity should be defined in terms of those aspects of behavior and daily life functioning that most disturb the person's quality of life and ability to continue functioning at pre-morbid levels, together with aspects that impact adversely on relationships with family, friends, and community. Since dementia is most essentially a disease of impaired cognition, the neuropsychologist would be likely to measure severity in terms of performance on tests of cognition. The basic scientist interested in pathogenesis and etiology might wish to define severity in a way that would reflect the extent and quality of fundamental brain lesions and neural dysfunctioning, perhaps measured using a combination of examinations for structural change and tests of brain functioning. It is generally acknowledged that these different approaches to severity correspond imperfectly with one another, and that the underlying purpose for measuring severity should determine how it is measured.

When the objectives of a research project include comparisons among groups or across different research studies, it is important that the means by which severity is assessed be as constant, objective, and unambiguous as possible. This is most important for criteria that distinguish mildly demented persons from non-demented individuals, since minor differences at this level may yield large differences in the number and characteristics of mildly demented individuals in the population under study.

The DSM-III-R criteria for dementia severity are as follows[55]:

Mild dementia. Although work and social activities are significantly impaired, the capacity for independent living remains with adequate personal hygiene and relatively intact judgement.

Moderate. Independent living is hazardous, and some degree of supervision is necessary.

Severe. Activities of daily living are so impaired that continual supervision is required, e.g. unable to maintain minimal personal hygiene, largely incoherent or mute.

In much of the older literature the terms (mild/moderate/severe) are used without adequate explanation, and it often appears that the examiner who made the diagnosis also indicated his assessment of severity using

one of these words without rigorous definition. Three examples of instruments that summarize severity in a composite way are the Cognitive Deterioration Rate (CDR)[60], the Global Deterioration Scale[61], and the Karasawa scale[62]. A modification of the CDR is currently in wide use in the US as part of the CERAD project[63]. The Global Deterioration Scale provides an extended scale for grading severity, but is often difficult to apply to atypical patients who may show asymmetric deterioration in the several aspects of cognition and behavior that serve to define each stage. The Karasawa scale, widely used in Japan, provides a measure quite similar to the CDR. Although they are very useful tools and the researcher cannot avoid using them, these unidimensional scales ignore the reality that the severity of impairments and disturbances is not uniform or symmetrical across cognitive, behavioral, orientational, personality, and neuropathological expressions of disease.

In some epidemiologic studies of dementia it is specifically stated that mild cases were included or excluded, or that the reported data are limited to cases of dementia that are severe, or moderate and severe. In some reports data (such as rate estimates) are reported according to mild, moderate, or severe disease. It is understood that severe dementia in these papers includes all cases that were severe or worse, i.e. including profound and terminal cases. In other studies it is implied that the case-finding method was expected to result in the identification only of cases of a defined level of severity, such as moderate or severe. In more recent studies, application of DSM-III-R criteria would be expected to yield cases whose dementia was sufficiently severe as to interfere with usual social or occupational functioning, but that are otherwise *un*selected for severity in any formal way. The DSM-III-R criteria are obviously intended to allow for the detection of at least some mild cases, since further criteria (see above) are provided to allow designations of mild, moderate, and severe. In an informal way, the DSM-III-R requirement that the person show *demonstrable* impairments in memory and at least one other cognitive domain implies the employment of threshold test scores to decide if performance is or is not impaired. Presumably, these thresholds are to be set so at least some mildly demented persons will score in the impaired range.

From an operational point of view, the researcher who wishes to use DSM-III-R criteria in a population-based study of dementia should do so with the knowledge that some (perhaps a substantial proportion but probably not all) of the true cases of mild dementia in the study population will be correctly categorized, i.e. case finding should identify mild cases and some, most of these should be true cases. While the sensitivity of case detection methods may vary markedly (across projects, with different methods, in different populations), it is likely that in any single project the sensitivity will be nearest 100% for severe dementia, and lowest for mild dementia. If the sensitivity and specificity of case-finding are reasonable, one would expect that a substantial proportion (probably the majority) of the persons identified as demented will be mildly impaired. If this is not the case, the researcher should be concerned that sensitivity may not be good even for moderate cases, leading to errors in rate estimations and to the identification of a case series that may not be representative even of the moderate and severe cases of dementia in the source population.Thus, it is valuable to assess severity even if the intent is to focus the research investigation on cases designated as moderate or severe. In prevalence and incidence studies limited to moderate and severe cases of dementia defined on the basis of DSM-III-R criteria, it would appear that the initial step should be to identify all cases meeting criteria, with the second step being an assessment of severity.

The problem of deterioration as requirement for diagnosis

The DSM-III-R diagnostic criteria for dementia *do not reflect* the common clinical understanding that the primary characteristic of a dementing illness is cognitive *deterioration.* As conventionally considered, dementia is a condition most essentially characterized by declines in memory and other aspects of cognition over a defined interval, generally at least 6–12 months. In some cases of dementia (commonly in CvDem) the cognitive disturbances develop in steps, or there may be an initial abrupt deterioration, followed by a plateau during which little or no decline occurs. In any case, the usual clinical diagnosis of dementia requires that the cognitive disturbances be acquired (onset more than 6 months previously but within the prior 10 15 years), that they progress or at least persist over a period of at least 6-12 months, and that they not be attributable to some other causes such as malignancy, severe trauma, or other obvious brain condition not ordinarily thought of as a dementing illness. These shortcomings of the DSM-III-R criteria for dementia are partially repaired by the DSM-III-R criteria for primary degenerative dementia (i.e. AD) and CvDem, since patterns of onset and progression are part of the criteria for these types of dementia.

If it is required that the impairments be acquired, it follows that judging if test performance suggested deterioration would be facilitated by considering information on education, occupation, culture, life experiences, etc. For example, if a person with normal intellectual capacity had only been allowed to complete 4 years of schooling, had little printed material for

reading, and had worked as a laborer all of his life, he would almost certainly receive lower scores on most cognitive function tests than would another person with more education and greater sophistication but similar intellectual capacity. Our interest in dementia is such that we would not ordinarily wish to classify the uneducated, unsophisticated person as demented unless his functional intellectual capacity had actually deteriorated. The implication of this course of reasoning is that 'demonstrable evidence' of a cognitive disturbance would be a matter of interpretation of test performance, taking into account relevant information available for that individual. Standardized methods of deciding if 'demonstrable evidence' of cognitive disturbance is present have not yet been developed in a form that will allow confident comparisons among nations, or even among different cultural, occupational, or education strata within nations.

A very important, unpublished observation is that for many of the individuals found in the course of community surveys who seem to be obviously demented, little or no history of deterioration is elicited. When the proxy informant is asked if the participant has any problem with memory or thinking, he or she often answers 'no.' Even with probing, many proxy informants deny that the participant has any problems with social or interpersonal activities, or with activities of daily living. Although this is most common for the participants who appear to be mildly demented, it is also true for a sizable proportion of those who are moderately demented. Part of the problem has to do with the fact that many older persons have retired, have few social interactions, are given no substantial responsibilities, and their families have accepted the idea that it is normal for aged people to cease many of the intellectual, social, and physical activities that had been a part of their lives at younger ages.

What instruments should be used to assess cognitive impairment?

Clinicians have been using mental status examinations for many years in the evaluation of dementia and delirium. In Japan and several other Asian nations, the Hasegawa scale has been widely used; an improved version of that instrument has become available recently[64]. In North America and Europe the mental status examination currently most widely employed is the Mini-Mental State Examination[65]. Other instruments in wide use include the Information-Memory-Concentration test[66], the Short Portable Mental Status Examination[67], the Modified Mini-Mental State Exam[68], the Neurobehavioral Cognitive Status Examination[69], and the Cognitive Capacity Screening Examination[70,71].

The CAMDEX and Geriatric Mental State (GMS) are comprehensive, structured interview schedules that include tools for collecting historical information as well as for evaluating the subject's cognitive functioning[72–74]. Both have been automated or semi-automated, and a computerized diagnostic system has been derived from the GMS. These systems have been widely used in comparative cross-national studies, and have sometimes provided the 'gold standard' diagnosis in the evaluation of other instruments.

Although it is a simple matter to translate tests from one language directly into another, the appropriateness of test items and the meaning of responses will vary in different languages and cultures. Further, the interpretation of test scores cannot be assumed to be symmetrical across cultures and may be strongly influenced by the examiner's training, experience and judgement. There are few if any tests of cognitive functioning that are 'culture fair' and for which scores and score ranges of comparable meaning across different education, language, and cultural groups have been defined. Even within communities there may be so much cultural, social, occupational, and educational heterogeneity that fair comparisons of rates of cognitive impairment across groups become impossible.

For the Ni-Hon-Sea-Tai project (see below), a committee of collaborating American and Japanese researchers created a composite instrument specifically for use in comparative cross-national research. That instrument, the Cognitive Abilities Screening Instrument (CASI) was developed under the leadership of Evelyn Teng and Kazuo Hasegawa by merging the MMSE, the Modified Mini-Mental State Exam, the Hasegawa Dementia Scale and a small number of additional test items. A Chinese language version for use in Taiwan has recently been developed and tested. The CASI is a 12–18 minute test designed to measure similar aspects of neuropsychological functioning in the US, Japan, and Taiwan by retaining essential structure, content, and scoring characteristics while allowing culture- and language-specific adjustments of specific items. With either computer-assisted or hand scoring, numeric scores are calculated for the entire CASI, the MMSE, 3MSE, and the Hasegawa Scale, as well as subscale scores across several cognitive domains (immediate memory, remote memory, attention, orientation, etc.). Validation studies of the CASI employing panels of demented and non-demented subjects have now been completed and data have been compared between Osaka, Tokyo, Los Angeles, and Seattle, and additional data are becoming available from community studies in Honolulu, Hiroshima, and Taiwan[75].

Although problems related to language and cultural differences are most obviously important for tests of cognitive functioning, similar issues are encountered with standardized instruments for assessment of physical functioning (self-reported activities of daily living, etc.),

depression, sensory functioning (hearing, vision, olfaction, etc.), and instruments used in interviews of a proxy informant or caregiver. The CATMOD/AGECAT instrument addresses some of these issues and has been translated into several languages. A particularly promising instrument for assessing deterioration by interview of an informant, the IQCODE, is being widely used but has not yet received careful scrutiny for the effects of language and cultural factors[76,77].

The problem of diagnostic misclassification

In most of the published reports comparing autopsy findings with premorbid diagnoses of AD or CvDem, there was agreement for 75–85% of cases, i.e. the diagnoses made during life were incorrect for 15–25% of cases[78–80]. When premorbid diagnoses of AD were not confirmed, the autopsy diagnosis was most commonly CvDem or mixed AD/CvDem. When premorbid diagnoses of CvDem were not confirmed, the autopsy diagnosis was most commonly AD or mixed AD/CvDem. Although some researchers are now claiming accuracies exceeding 90% (ref. 81), other groups continue to report diagnostic accuracy in the range of 80% (refs. 82, 83). Such diagnostic accuracy estimates are generally based on individuals who were referred to a neuropsychiatric diagnostic clinic or center because someone suspected the diagnosis. Further, the clinical diagnosis was often established after months or years of intensive evaluation and follow-up. Although diagnostic accuracy has not been adequately assessed for cases categorized during the course of a community survey, it would probably be substantially lower than for referred cases. If diagnostic accuracy for cases identified in a community survey is 75% (i.e. only slightly lower than for cases referred to and evaluated in neuropsychiatric and geriatric diagnostic facilities), one of four diagnoses will be incorrect. Such a severe endpoint misclassification could have a serious adverse impact on rate estimates and on the power risk factor studies.

A second factor that may reduce the power of a research project to detect true risk factors is the occurrence of subclinical disease in persons classified as controls. This problem will be especially severe when the risk factor being evaluated is thought to act through an association with the processes leading to neuropathologic abnormalities (neuritic plaques, neurofibrillary tangles, etc.), and when the cases and controls are older (75 + years). If, as commonly believed, only a fraction of persons with the characteristic neuropathological changes actually have the clinical disease, it follows from age-specific prevalence estimates given elsewhere that a rather large proportion of 75–85 year old controls will be incorrectly classified as disease-free. Thus, the problem of end-point misclassification of both cases and controls may weaken the study's power to detect true risk factors for AD and CvDem. The only remedies to these problems are to maximize the number of cases and controls in the study while minimizing misclassifications by careful validation of disease in cases and non-disease in controls by longitudinal follow-up evaluations and autopsy in the case of death.

Endpoint misclassification problems are also important in research and at the identification of risk factors for CvDem. Since we envision CvDem as developing in persons who have had strokes, the demonstration of an association of CvDem with risk factors for stroke should be no surprise. The more important question involves what factors are associated with the development of dementia given that one or more strokes have already occurred. Possible factors might include locations of the infarctions (size of vessels involved; architecture of vessels; embolism vs thrombosis), neural reserves and neuropsychologic adaptability (possibly associated with education, occupation, handedness, language facility, cognitive style), how large or numerous the strokes are, and how rapidly additional strokes develop (basic risk factors for stroke, especially those involved in multiple small strokes). The selection of controls for such studies is as crucial as the selection of cases.

Cross-national epidemiologic research projects — Examples

WHO study of age-associated dementias (program on aging)

This project involves six countries: Canada, Chile, Malta, Nigeria, Spain and the United States. Its goals are to define age-specific prevalence and incidence rates for a rural and an urban community in each participating nation, for dementia of all causes, and for Alzheimer's disease and vascular dementia. The underlying scientific purpose of this effort is to identify cross-national, cross-community, and/or urban rural differences and patterns that may illuminate new risk factors, thereby leading to an improved understanding of the development of these illnesses.

The project is managed from the WHO Project on Aging office, located at the National Institute on Aging, Bethesda, Maryland, and headed by Stefania Maggi. Scientific direction is provided by a Steering Committee of international experts, and operation is coordinated by the Studio Multicentrico Italiano sulla Demenza, in Florence, Italy, headed by Luigi Amaducci.

Key design elements include the following[84]:

- At each site, work will progress in three steps: (1) standardization, (2) pilot study, and (3) field study.

- The field study will progress in three phases: Phase 1 - population selection, enumeration, sampling, interview to obtain risk factor information, and testing of participants with a dementia screening test, Phase 2 - confirmation of cognitive impairment by additional participant testing and interview of a proxy informant, progressing to diagnosis of dementia with exclusion of cases of depression and mental retardation; Phase 3 - diagnosis of dementia subtypes (AD, CvDem, etc.).

- All instruments will be translated into the appropriate language with individual test items adapted to local cultural and education contexts.

- The dementia-screening test will be either the Mini-Mental State Exam or the Information-Memory-Concentration test, depending on the results of standardization and pilot testing.

- For each community the target population will be men and women aged 65 and older, both non-institutionalized and institutionalized. The maximum acceptable non-response rate has been set at 10%.

- To examine cross-site observer agreement, 30 case records will be fully translated and subjected to independent diagnostic evaluation at each site. Similar case reviews using videotaped examinations and interviews will also be carried out.

- The diagnosis of dementia will require that the case fulfill both DSM-III-R and ICD 10 criteria.

- 100% of the participants who fail the Phase 1 screening test and 10% of those who pass it will receive the Phase 2 evaluation.

- Phase 2 instruments will include the CAMDEX neuropsychological examination and structured interview with a proxy informant, an Activities of Daily Living Scale, and a functional questionnaire.

- Borderline cases with cognitive impairment but who do not fully meet diagnostic criteria will be re-evaluated after 6 months.

- Subjects diagnosed as demented will be re-evaluated after one year to define the natural history of the disease.

- To estimate incidence rates and examine prospectively ascertained risk factors, all non-cases will be reassessed after one year by means of the same multiphase procedure.

- In arriving at clinical diagnoses, test scores will be interpreted with use of different age- and education-adjusted cut points.

Major aspects of standardization have been accomplished and the study is now in its pilot phase. Data from pilot studies will be presented in November 1992. The field phase is expected to begin in spring 1993.

Indo-US cross-national dementia epidemiology study

This project is funded by a research grant from the National Institute on Aging to the University of Pittsburgh. It is a collaborative project with the Centre for Ageing Research in India (CARI) located in New Delhi. The Principal Investigator is Mary Ganguli, with *CARI staff members including Vijay Chandra (Co-*Principal Investigator), Lalit M. Nath, Arun Mehta, Rajesh S. Pande, and Sujatha D. Sharma. Long range research plans include a community survey of dementia in a rural community near New Delhi, with the objective being a comparison of rates, clinical patterns, and correlates of dementing illnesses in that community with similar information from an American community near Pittsburgh where an epidemiologic study of dementia has been underway for five years. Current work is focused upon developing and testing instruments and methods for the assessment of cognitive and physical functioning. The immediate goals are to develop methods that will be acceptable to the older, residents of the community, that will provide valid measures of cognitive and physical functioning, that will allow application of standardized diagnostic criteria for dementing illnesses, and that will be comparable to the instruments, methods, and criteria used in the US project. Although illiteracy, cultural, and language differences have posed very difficult problems, some anticipated and others unexpected, excellent progress has been made and candidate instruments in Hindi are being evaluated[85].

The EURODEM project

A conjoint, co-operative analysis of data sets from 12 selected epidemiologic studies in Europe during the late eighties was recently carried out to examine cross-national patterns of prevalence, and to assess risk factor associations[86]. The results of cooperative analysis with pooled data showed the prevalence of dementia to be slightly greater for men below age 75 and slightly greater for women after that age. Although a rather wide range in age-specific prevalence rates was observed across studies, all 12 datasets showed an approximately exponential increase in prevalence with advancing age. The overall European prevalence values for five-year age groups from age 60 to 94 years were 1.0, 1.4, 4.1, 5.7, 13.0, 21.6 and 32.2%. Several of the research teams that cooperated in these analyses are currently collaborating in further cross-national epidemiologic studies of prevalence, incidence, clinical course, and risk factors for dementia, AD, and CvDem.

The NI-HON-SEA-TAI project

This project is a cooperative effort to compare rates,

clinical characteristics, risk factors and correlates of AD and CvDem in Japan (NI-), Honolulu (HON-), Seattle (SEA-), and Taiwan (TAI). The studies in Honolulu and Seattle are focused on older Japanese–American citizens. This will allow comparisons between Japanese-ancestry persons still living in Japan, migrants to the American mainland (Seattle), and migrants to Hawaii, a site geographically and culturally intermediate between Japan and the western world. The impetus for these projects was the reported difference in rates of AD and MID between the US and Europe and Asian nations (see rates, above). The central goals are to determine if these differences can be confirmed using comparable methods and, if so, to investigate the influences of genetic factors, nutrition, culture, language, etc. on the occurrence of these disorders. It is hoped that the findings will shed light on the roles of genetic versus environmental factors in the development and progression of these diseases. The recent addition of collaborating projects in Taiwan represents an underlying intent to extend the methods developed initially for cross-national comparisons between the US and Japan to additional comparisons with other nations and cultures. All of the fundamental instruments and methods in use in this project were developed with this ultimate intent[87].

The principal cooperating institutions include the Radiation Effects Research Foundation (RERF, Hiroshima), St. Marianna University School of Medicine (Kawasaki City), the Tokyo Metropolitan Institute of Gerontology, the National Cardiovascular Center (Osaka), National Taiwan University, Taipei Veterans General Hospital, Kaohsiung Medical College, the University of Washington, the University of Hawaii and Kuakini Medical Center, and the National Institute on Aging. The Honolulu project began in March 1991 and the Seattle project got underway in June 1992. A third study began in 1992–93 in the adult health study cohort of the Radiation Effects Research Foundation. Preliminary surveys are beginning at two sites in Taiwan. Instruments have been developed and pretested at each of the cooperating sites, and at the National Cardiovascular Center in Osaka, the University of Southern California, the University of Michigan, and the University of Hawaii.

The following strategies to improve comparability have been agreed upon by project collaborators:

- Surveys will be done in community-representative and/or fully defined, older populations without excluding individuals residing in institutions, special housing situations, or long-term care facilities.

- An effort will be made to assess patterns of in- and out-migration in study populations. Stable populations will be used whenever possible.

- The initial phase of surveys will involve an assessment of cognitive functioning of all participants. Results will be used (by screening or stratification and sampling) to define which persons will receive the algorithmic and clinical evaluations.

- The Cognitive Abilities Screening Instrument (CASI) will be used as the primary tool to measure and characterize cognitive functioning. Persistence of cognitive impairment will be ascertained by administration of the CASI at least twice.

- The fact, quality, and extent of cognitive and functional deterioration will be assessed using the IQCODE, a modification of the Blessed Dementia Rating Scale, and a small number of questions asked of a caregiver or proxy-informant related to recognition of problems with memory and thinking.

- The process of dementia case-finding and diagnostic categorization will take place in three phases: (1) an initial screening or baseline testing of cognitive function, (2) an algorithmic classification step based on a limited amount of highly standardized data, and (3) a clinical evaluation corresponding to local standards – without standardization other than reference to DSMIII or ICD criteria.

- An effort will be made to substantiate diagnostic categorizations by observation of the clinical course for a period of at least two years, or by autopsy.

- All diagnostic categorizations will be essentially based on DSMIII or ICD-10 definitions and criteria; however, certain modifications of these are anticipated.

- Data will be collected and analysed to allow cross-national comparisons of sex- and age-specific prevalence curves for dementia (all-cause), Alzheimer's disease, and vascular dementia; although mild cases will be studied, the principal cross-national comparisons will be of severely and moderately demented persons.

- Cross-national comparisons will be primarily based on the algorithmic classification; for these comparisons, the endpoints will be moderate or severe acquired, persistent cognitive impairment, with or without evidence of cerebrovascular disease, and with or without evidence of parkinsonism.

- Comparisons will be made independently at each site between the algorithmic classification and the clinical diagnoses of dementia, AD, CvDem, and mixed AD/CvDem; patterns of these within-site relationships will then be compared across sites.

In most surveys for dementia the study design involves follow-up of individuals who fail a screening test, with few or none of those who pass the test receiving a full evaluation for dementia. This requires either an assumption that false negatives are negligible (very high

sensitivity), or actual knowledge of sensitivity *of the specific screening test at the cut-point used and in the population in which it is used.* Calculation of test sensitivity based on panels of volunteer cases and controls will not necessarily reflect the test's sensitivity in community surveys, since the cases tend to be more clearly ill and controls tend to be more clearly normal than the cases and non-cases identified during the course of a survey. In Honolulu and Seattle, these problems are addressed by using the baseline CASI score to stratify the population into three exhaustive and mutually exclusive sampling strata (poor, intermediate, and normal performance) from which random samples are then drawn to receive the full dementia evaluation. This strategy represents an alternative to the standard screening test approach. By using sampling fractions of 100%, 33%, and 7% in the three strata, a sample is drawn that represents approximately 20% of the baseline population, of whom approximately half are poor performers, one-quarter are intermediate performers, and one-quarter are normal performers. By shielding the follow-up examiner from knowledge of the individual's baseline score it will be possible to examine sensitivity, specificity, concordance of scores, etc. without bias. By carrying out future analyses with the use of sampling weights it will be possible to project all results to the original population, thereby avoiding the problem of uncertain sensitivity of a screening test.

What is the scientific rationale for cross-national comparative studies of dementia?

The primary answer to this question is that cross-national differences may provide clues concerning causes and pathogeneses. Some differences in rates of vascular dementia are to be expected, given that we already know that substantial differences in stroke rates and types of stroke exist between cultures and among nations. It seems a reasonable assumption that prevention of vascular dementia will follow automatically when we prevent strokes, and that dementia, like other clinical signs of stroke, is more a function of where the stroke occurs (what brain tissue is infarcted) than of the fundamental cerebrovascular pathology that underlies the disease process. Further, we already know much about the prevention of strokes, and the incidence of many kinds of stroke has decreased precipitously around the world during the last two decades.

In contrast, AD is conceptualized as expressing a diffuse disease process whose determinants and pathogenesis are poorly understood. We generally expect that prevention of AD is likely to require prevention or retardation of the underlying process. It also seems likely that the underlying process is not a unitary one, but is comprised of several subprocesses interacting in parallel and in sequence, with each such subprocess being influenced by different genetic and environmental factors, but with the final expression being recognized as Alzheimer's disease. Although it is reasonable to look to epidemiologic research for clues, research to date has illuminated very few risk factors – in fact, only age, a family history of dementia, and head injury have been consistently implicated as influencers of the development of AD. Cross-national differences in the prevalence or incidence of AD certainly represent very promising avenues toward defining new risk factors, and thereby toward understanding the pathogenesis of AD.

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