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SPECIAL ARTICLE

Studies of the epidemiology of dementia: Comparisons between developed and developing countries

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ABSTRACT. By the year 2025, 68% of the world's population aged 65 and above, nearly 277 million people, will be residing in developing countries. The less industrialized nations have been the least studied to date, and may yield significant new information about the etiology and risk factors for Alzheimer's disease (AD) and other dementias. Although it is readily apparent that cross-national and cross-cultural comparisons are desirable, these can be meaningful only if based on comparable methodology. In this work we will discuss some general conceptual and methodological issues regarding epidemiological studies of dementia in developing countries. The topics discussed include community-based screening for dementia, screening instruments and their application in cross-cultural studies, steps in standardization of new or modified neuropsychological tests, and some special considerations in studying uneducated/illiterate populations.
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INTRODUCTION

By the year 2025, 68% of the world's population aged 65 and older, nearly 277 million people, will be residing in developing countries (1). A few publications in literature and a larger body of anecdotal information from non-Western, less industrialized countries, e.g., India (2) and Nigeria (3), suggest that Alzheimer's disease (AD) is unusual in these countries, and that the pathological changes characteristic of this disease are rarely found in autopsy brains (4, 5). The extent to which these findings are representative of the general population is unknown. Large community-based epidemiological studies have yet to be published from these countries with the exception of the People's Republic of China (6).

The less industrialized nations have been the least studied to date, and may yield significant new information about the etiology and risk factors for AD and other dementias. In 1988 the National Institute on Aging (U.S. Department of Health and Human Services) announced a programme on cross-national investigations of the epidemiology of AD in consideration of the fact that: "Other countries, cultures, ethnic or population groups, with different exposures and habits, may offer clues to the etiology of the disease that are not apparent in Western industrialized na-

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tions. The need to search more aggressively and widely for potent modifiable risk factors requires movement beyond national boundaries" (7). Several potential research questions were addressed, including age-specific incidence and prevalence rates of AD in defined community-residing populations, and whether these rates varied according to geographic, genetic, ethnic, socioeconomic or other characteristics of countries or regions, or by sex, educational level, dietary habits, injuries, exposures, or other characteristics between countries or within countries in distinct subpopulations.

Differences in dementia occurrence rates in various societies will help to indicate where to search for risk factors and etiological clues (7, 8). If the prevalence of AD is similar to that in developed countries, the developing countries, with their increasing life-expectancy, must prepare for an "approaching epidemic" (9) of dementia such as that now emerging in the developed nations.

If the overall prevalence of AD is in fact lower than that in the West, it must still be determined whether age-specific prevalence itself is low or whether lower overall prevalence is a function of currently shorter life-expectancy in developing countries. If age-specific prevalence is low, it remains to be seen if the age-specific incidence of new cases is also low, or whether it is equal, but prevalence is lowered by the higher case fatality ratio in the developing countries which shortens the duration of AD. Furthermore, whether or not the rate difference apply to secondary dementias as well must be determined. It has been reported that these other dementias may be as or more common in India than in the West (2).

Finally, it is important to determine the amount of rate variation accounted for by selection factors and other methodological differences. Such differences must be identified and limited, if not eliminated, if we are to develop a more useful understanding of the global epidemiology of AD.

Although cross-national and cross-cultural comparisons are desirable, these must be based on comparable methodology if they are to be useful. Operationally defined and reproducible diagnostic criteria are required, as well as reliable, sensitive screening instruments. These measures must be as unbiased as possible by culture, education, and socioeconomic status. To be practical in a large number and variety of countries, measurement tools should lend themselves to reliable administration by paraprofessionals and trained non-professionals. Comparisons with existing studies in Western nations will be facilitated by the use of measures identical or similar to those already employed in such studies. It cannot, however, be assumed that the validity of these measures is equal in all populations. Whether cross-cultural comparisons are based on data from previous, ongoing, or new studies specifically designed for such comparisons, or from a combination of new and ongoing studies, decisions about the measurement of critical variables should not be made lightly.

In this work we will discuss some general conceptual and methodological problems regarding epidemiological studies of dementia in developing countries. In subsequent publications we will report the results of our Indo-US Cross-National Dementia Epidemiology Study. The present work is divided into five parts: Part 1) briefly summarizes previous cross-cultural/national studies of dementias; Part 2) lists some methodological problems regarding studies of dementia in developing countries; Part 3) discusses community-based screening for dementia, including screening instruments and their application in cross-cultural/national studies; Part 4) describes the steps in standardizing new or modified neuropsychological tests; and Part 5) discusses some special considerations regarding illiterate populations.

PREVIOUS STUDIES REPORTING CROSS-CULTURAL/NATIONAL AND ETHNIC COMPARISONS OF DEMENTIAS

Japanese and Russian publications show a significant prevalence of vascular or multi-infarct dementia (MID) over AD, while all other studies show either an excess of AD or no difference (10, 11). The preponderance of vascular dementia over AD is consistent with the higher stroke rate in Japan (12-14). Serby et al. (15) also reported more MID than AD in an American-Chinese nursing home population, although Zhang et al. (6) reported that AD was the predominant cause of dementia in an elderly Chinese population in Shanghai. Schoenberg (16) found

higher age-adjusted prevalence rates of severe dementia in African-Americans than in Caucasians in Copiah County, Mississippi, with the preponderant cause being AD. Treves et al. (17) suggested that the incidence of "presenile dementia" in Israel was higher among Ashkenazi Jews than among Sephardic Jews. Secondary dementias were more common than AD in a small sample of Cree Indians (18) in Canada.

It has been argued that the *total* prevalence of dementia in the community may be *lower* in developing countries than in the West because life-expectancy in general is shorter and dementia itself is a cause of premature mortality (19). In industrialized nations, it has been hypothesized (20) that the prevalence of dementia is higher in communities where demented elders are less likely to be placed in nursing homes. As the practice of institutionalizing relatives is socially unacceptable in most developing countries, and there are usually no long-term care institutions, their *total* prevalence of dementia may be *higher*.

Vascular dementia is associated with a shorter survival rate than is AD (21). Although there is a significant risk of dementia after stroke (22), high acute mortality from stroke may in fact reduce the prevalence of vascular dementia in developing countries. Causes of dementia less common in the West, e.g., hypothyroidism, B_{12} and other vitamin deficiency, neurosyphilis, protein-calorie malnutrition, may be much more prevalent in the poorer and medically underserved rural populations. In the developing world alcohol and tobacco use is quite different in nature and extent from that seen in Western societies. Occupational exposures are different and much less stringently regulated. Infectious diseases (e.g., malaria, tuberculosis, hookworm infestation causing chronic anemia) continue to be prevalent. Chronic diseases in the elderly are less uniformly and aggressively treated than in the West. Any of these factors may affect the prevalence rate of secondary dementias in the community.

There may also be considerable difference in the course and outcome of dementia between the developing and Western countries. While the rural poor in developing countries do not usually seek help for dementia, it is a common phenomenon in private urban practices of neurologists and psychiatrists. This discrepancy may reflect not only referral bias, but also perhaps survival bias among the poor. The community's expectations of the elderly are low, and many potentially treatable sources of disability, including memory loss, are tolerated as part of normal aging. As a result, there is under-reporting and non-intervention even when the latter might carry a major benefit, such as in some secondary dementias, potentially leading to worse outcomes. On the other hand, care-giving is uniformly provided by families, eliminating the adverse effects of institutionalization.

METHODOLOGICAL APPROACHES IN STUDIES OF DEMENTIA IN DEVELOPING COUNTRIES

Epidemiological studies of dementia in developing countries raise many methodological issues:

(1) Well-defined study populations are rarely available with adequate numbers of elderly people, the group at highest risk for dementia. Thus, although cases may be identified, population-based indices of disease occurrence cannot be calculated.

(2) Many elderly people do not know their exact ages and may give differing ages at different times. Since the incidence and prevalence of dementia increases exponentially with age, lack of information on age affects reporting of age-specific rates.

(3) A fatalistic attitude about aging and resignation to ill health in old age makes the elderly and their families reluctant to seek medical help. Thus hospital statistics substantially underreport dementia.

(4) Limited qualified medical personnel who are generally over-worked and inadequately trained in geriatrics will rarely spend time to detect dementia or to come to a diagnosis of AD.

(5) Since potential cases of AD rarely seek medical help, and may not be properly diagnosed when they do, reliable data can only be obtained from door-to-door screening of an entire community. This requires substantial time and effort.

(6) An adequately standardized instrument is seldom available for screening an entire community by lay health workers. Instrument stan-

dardization requires a major investment in time and money before a study can be carried out in such a population.

(7) Early diagnosis of AD is essential if the incidence rate is to be established. This remains a difficult task world-wide.

(8) Early mortality in patients with AD (usually from pneumonia, hip fractures, or diarrhoea) makes advanced cases a rarity in the community. These cases are usually the most "apparent" and identified in prevalence surveys. The lack of such cases leads to the erroneous belief that the prevalence of dementia is "low".

(9) Detailed, reliable family history of illness is rarely available making it difficult to study possible risk factors.

(10) Medical records are virtually non-existent and rarely mention dementia or cognitive dysfunction, and exposure to risk factors is poorly documented. Retrospective studies therefore, are not informative.

(11) The currently elderly cohort in most developing countries is not highly educated and may contain a substantial proportion of illiterate individuals. Such persons may be the least likely to recognize and seek help for memory loss. In addition, they pose particularly difficult challenges for the diagnosis of dementia, as will be discussed later.

(12) Samples used for cross-cultural/national comparisons vary in their source, ranging from "convenience samples," and speciality clinics or ward populations to community samples. It may not be possible for all centres in a cross-cultural/national study to sample in exactly the same way, but differences should be carefully examined to determine their potential impact on the results of the study.

Meaningful epidemiological estimates and comparisons require that samples be representative of the population from which they come and to which the results will be generalized. Random samples, stratified or otherwise, will provide the most valid information; however, in countries where there is no readily available master list of all citizens, a door-to-door census of the target population will be necessary before such a sample can be drawn. Additional problems arise, for example, when dwelling units do not have street addresses or are widely scattered over a large geographic area. If resources are adequate, it may be feasible to select a community for study and sample all households. Ideally, a community with low rates of in- and out-migration should be selected. In developing countries, seasonal and recreational travel by the elderly is likely to be low, making them potentially available for study all year round. Care must be taken not to introduce a systematic bias into the sample by excluding subgroups that are more difficult to reach. Required sample sizes should be estimated on the basis of calculations of the statistical power needed to test the hypotheses of interest, in consideration of the projected prevalence and numbers of variables to be examined.

(13) An advantage of conducting epidemiological studies in developing countries is that the elderly population's rates of cooperation with research, particularly if it includes some degree of free health care, is likely to be high compared to that seen in developed countries. Ethical standards must be maintained during recruitment, so that advantage is not taken of an elderly individual's lack of education and sophistication. Consent forms should be locally comprehensible and be read and explained to subjects who cannot read or understand them. In some traditional societies, it is preferable to obtain consent to participate not only from the potential subject but also from the head of the household, appropriate community leaders, etc.

(14) Incentives for participation should be attractive but not such as to be coercive or cause resentment within the community. Sometimes incentives provided to the elderly are appropriated by other family members. Investigators must become familiar with local concerns, customs, and preferences.

COMMUNITY-BASED SCREENING FOR DEMENTIA

Cognitive decline

Cognitive decline, characteristic of dementia, is measured objectively by standard neuropsychological (cognitive) tests, preferably at two or more points in time. In the absence of prospective data, cognitive impairment is operationally defined for prevalence studies as test performance below a specified level or cut-off score

(cutpoint). However, factors other than dementia can affect cognitive test performance. Cognitive functioning is a product not only of brain structure and physiology, which it is assumed do not vary between populations, but also of knowledge base, acquired skills, etc., which are clearly affected by culture and education. It is therefore difficult to measure "brain functioning" independently of the effects of culture and education. Tests of general and specific cognitive functioning which are standardized in, and appropriate for, members of one culture may be inappropriate in another. Thus, when selecting or designing cognitive tests to detect dementia in a given population, the scope of the cognitive function(s) being measured should be the overriding consideration guiding the form and content of the task. Floor effects (majority of population performing close to the minimum score) can affect the usefulness of the test as a screening tool for dementia; ceiling effects (majority of population achieving close to the maximum possible score) may be less problematic for detecting dementia but do not allow optimal grading of performance. Norms for the test(s) should be known or established for a given population before the test is used to separate potentially "abnormal" (e.g., demented) persons from their "normal" peers.

A related issue is the difficulty, even in well-studied populations, of distinguishing the effects of "normal aging" from those of incipient or mild dementia (23, 24); screening for moderate and advanced cases of dementia is easier. Test performance can also be influenced by environmental influences (such as distractions, drug effects, etc.) and random fluctuation; these factors can be detected by the experienced clinician but not by lay workers during population screening. Sensitivity and specificity of cognitive tests are therefore critical issues in dementia screening, particularly in (prevalence) cross-sectional studies in which cognition is assessed only once.

The challenge for screening is even greater in incidence (prospective) studies. To identify potential new (incident) cases, repeated evaluations are required to document transition from normal to impaired. The measurement tools must be sensitive to detect subtle and early changes over time; and norms for change must be determined.

Functional decline

Scores on cognitive tests should also be viewed in the context of their clinical significance. The DSM-III-R (25) diagnostic criteria for dementia include the requirements that impairment be present in at least two cognitive domains, including memory, and that the impairment be sufficient to interfere with normal social and occupational activities. Such interference with daily functional ability may help to distinguish between dementia and normal aging, as well as between "true" cognitive impairment and impairment limited to performance on tests. Ideally, therefore, screening for dementia should have a two-pronged approach, and be aimed at detecting both cognitive and functional disability. However, functional ability (activities of daily living or ADL) screening is a complex issue, since disability is a function of two highly variable factors: the individual's previous ability, and the demands of his/her daily activities. If there is co-existing physical disability (e.g., blindness or arthritis) which can by itself interfere with functioning and is not optimally corrected or treated, as often happens in developing countries, it can add to the impairment due to dementia. It may be difficult to distinguish between disabilities due to cognitive deficit and those resulting from co-existing physical impairments; however, these distinctions should be attempted when rating the severity of dementia. Furthermore, ADL scales developed for one population may be grossly inappropriate for another, particularly in comparisons between developed and developing countries. While ADL should be measured in potentially demented subjects, it may be ineffective as a screen for dementia and less than meaningful in direct cross-cultural/national comparisons. These issues will be addressed further in a separate manuscript (Fillenbaum et al., in preparation) on the development of an ADL scale for an elderly rural population in India.

COGNITIVE SCREENING INSTRUMENTS

Since resources do not exist to provide skilled clinical evaluation for dementia to all elderly individuals, some kind of screening process is required to set apart those who appear to require

such an evaluation. The primary function of a screening instrument is to identify individuals with the highest probability of having the disorder of interest (in this case, dementia). Those who result "positive" must then undergo one or more levels of increasingly definitive assessment which serve as the "gold standard" diagnosis for the disorder. Expert clinical manpower is usually reserved for evaluating those referred, on the basis of screening results, for definitive diagnosis.

Where resources are limited, as in developing countries, screening is often carried out by non-professionals or paraprofessionals. Screening instruments which are to be utilized by lay health workers, for example, must be sufficiently standardized and structured, and screeners adequately trained, to ensure reliable and valid screening.

To avoid "missing" even a single case of dementia, the instrument will probably select a large number of non-cases (false positives). For any given disorder in a given situation, it is necessary to weigh the relative cost of missing a case (i.e., false negative) against that of providing the detailed assessment of a non-case (i.e., a false positive), i.e., to decide on the appropriate balance between sensitivity and specificity. A cutpoint on the screening instrument must be selected based on this decision, which itself is largely predicated on the availability of resources.

Screening is usually accomplished by means of a global cognitive scale, such as the Mini-Mental State Exam (MMSE) (26), the Short Portable Mental Status Questionnaire (SPMSQ) (27), or the Blessed Information, Memory, Concentration test (IMC) (28). The MMSE is perhaps the most widely used, having been modified and translated into Chinese, Finnish (29), Korean (30), Japanese (31), Yoruba (31), Spanish (32), Cree (33), and Hindi (34). Although the translated versions of these instruments have been published, the effects of adaptation and translation on the psychometric properties of the revised instrument have not, to our knowledge, been reported except for the Hindi version (34). The results of studies using these modified instruments may thus not be completely comparable with one another.

A global or general mental status scale has the obvious advantages of being relatively quick to administer, and of tapping several relevant cognitive domains, albeit briefly. The sensitivity and specificity for dementia of such a scale, when used as a screen in a given population, will depend on the distribution of scores in that population and the cutpoint(s) selected for use in that population. It is possible that different cutpoints on the same scale can be used for different populations or different subgroups (e.g., educational strata) of the same population (6).

The use of additional tests, tapping a larger array of cognitive functions, would be more time-consuming but also allow more detailed characterization of cognitive functioning than would a single global scale. Thus, it would be expected to increase sensitivity, although at some cost to specificity. However, in a rural community-based study in the U.S. (35, 36), the use of a wider array of tests, with population percentile-based cutpoints, was found to increase sensitivity (over the MMSE alone) without decreasing specificity. In the same population, it has been found that adjusting test scores for level of education, as suggested by Kittner et al. (37), did not affect sensitivity and specificity overall; however, it improved sensitivity slightly in the most educated subjects and improved specificity in the least educated subjects (Belle S.H., personal communication). Thus, the same test score may have different implications in different population groups.

CROSS-CULTURAL / NATIONAL COGNITIVE SCREENING STUDIES

Several planned and ongoing cross-cultural/national studies [Ni-Hon-Sea (31), Ibadan-Indianapolis (31), WHO Age-Associated Dementia project (38), WHO Mental Health Program, (personal communication, Ustin T.B. to Ganguli M.)] were designed as *de novo* comparative studies, with screening batteries developed for the specific purpose of comparing different populations. Such projects are ideal because the design and selection of tests is thus limited to those which can be used simultaneously in all the target populations. Such multi-centre projects are very expensive and require massive efforts to organize, coordinate, and monitor. In more restricted circumstances, it might be practical to design add-on studies to ongoing projects as resources become available. Lessons learned from the origi-

nal study (e.g., about sensitivity and specificity of different tests) can be applied to the add-on project. The disadvantage is that tests already in use in the original study may not be suitable for the add-on study because of cultural/linguistic and educational differences between the two populations. Thus, the tests may require some degree of modification.

Regardless of whether a cross-cultural/national study is being designed *de novo* or as an add-on project, certain conceptual considerations apply to the design of the cognitive screening battery. The requirements for developing such instruments are several.

1) They should have acceptable levels of sensitivity and specificity for dementia. If the results of different studies are to be compared and diverse instruments are being used in these studies, these must have the same sensitivity so that the proportion of total cases identified is identical. Variation in specificity is acceptable and does not affect the final prevalence rates.

2) They should be reliable and valid when administered by individuals likely to be employed as field staff (screeners or testers) for the study.

3) They should be as "fair" as possible to the culture/ population to be studied.

4) The tests should, after modification, continue to be psychometrically sound.

5) Finally, they should facilitate meaningful comparisons between or among the different populations being tested. This last objective may be the most difficult to achieve.

Translation of the tests into a different language is, in some ways, the easiest modification. The essential steps are translation of the tests and instructions by one bilingual group and back-translation by another to ensure accuracy. This is followed by pre-testing in representative subgroups of the target population to ensure that the test and instructions are understandable. The pretesting also allows dialectical variation to be addressed and draws attention to other logistic and conceptual issues which might pose obstacles to screening of the given population.

Ideally, the test or test batteries used in the two populations should be identical. When this is not practical, they should be analogous, that is, they should tap similar cognitive domains using tests of analogous difficulty which involve, where possible, similar task demands. In doing so, the initial step should be an *a priori*, conceptually sound attempt to distill the cognitive functions tapped by each test and, particularly, to identify the cognitive impairment or weakness that typically limits a subjects' ability to perform the task in question. Thus, for example, the task of oral repetition (immediate learning and delayed recall) of words presented in a printed list involves functions including visual acuity, literacy, bucco-facial praxis, etc. However, the limiting factors in performance in an average elderly individual are impaired immediate (primary) and recent (secondary) memory, i.e., the test is primarily one of memory and not of visual perception, reading ability, or speech. In modifying the word list recall test for use in a study of an illiterate population, the primary aim should be to ensure that memory function remains the main factor determining the test performance. Thus, the words can be read to the subject, rather than requiring him/her to read them, without interfering too greatly with the goal of testing memory.

The next step is to check how well the tasks have been matched by observing individuals in the target population perform the task, listening to their feedback, and examining their scores. If preliminary observations and data suggest that these subjects are achieving lower scores because of some difficulty other than the cognitive function of interest, testers should evaluate if the test can be modified in some other way or if it should be deleted from the battery. If the former is the case, the prime consideration should remain ensuring that the modification still permits the desired cognitive assessment; and if the latter, the question becomes whether a different test of the same cognitive function(s) should be substituted, or whether dementia can be effectively screened for without assessing the function(s) tapped by that particular test.

In some cases where the task demands have been rendered as similar as possible, the distribution of scores in the two populations may still be markedly different. At this point, it would be reasonable to attempt to change the difficulty of the task without changing its character.

The instruments should be pre-tested and modified as many times as necessary, in successive small groups of elderly subjects, until the

tests appear to have the desired levels of difficulty, acceptability, and comprehensibility. They should then be pilot-tested in a representative sample to determine the distribution of scores on each test in the population, and to compare this distribution among the different cross-cultural/national populations being studied. Essentially, it is desirable to secure score distributions sufficiently similar that the range of measurement is similar in the various groups being compared. By "similar scores" in this context we do not mean that scores need necessarily be numerically equal on all tasks, since, as White (39) points out, scores can be calibrated separately for different cultural settings just as they are frequently adjusted for different educational levels or age groups. For example, when testing praxis in illiterate subjects who have never used writing implements, it is unrealistic to score their drawings by the same standards developed for those with a formal education. Potentially, partial credit can be given if reliable operational criteria can be developed based on normative data from the same population. Scoring criteria can be made less strict for such a population, but should not be loose and open to a variety of interpretations. In particular, floor or ceiling effects should not be *more* marked in one or other population because they will hinder attempts to define comparable cutpoints in the two populations at the lower or higher ends of the distribution.

If possible, an attempt should be made to test the validity of the modified tests by administering them to groups of non-demented, mildly demented, and moderately demented individuals. Scores on the tests should be able to discriminate among these groups. However, it may be difficult in developing countries to assemble a large enough sample of already diagnosed cases of dementia with varying levels of severity. In this situation, it becomes necessary to depend on the known validity of the original tests, the face validity of the modified tests, and the determination of norms on the modified tests in the standardization sample.

Once these requirements have been met, the screening instrument can be field-tested in a larger standardization sample, along with the "gold standard" diagnostic evaluation, so that sensitivity and specificity can be determined and optimal cutpoints selected for the final survey, as discussed in the next section.

In matching test batteries in this way, the implicit assumption is that the underlying structure of cognition is similar in the two populations, and that differences in their test performance reflects the varied degrees to which basic cognitive skills are developed through education, culture, and the demands and customs of the two environments in which the populations live. In this regard, a particularly difficult problem is posed by elderly populations in developing countries which are illiterate and without formal education.

STANDARDIZATION OF NEW OR MODIFIED NEUROPSYCHOLOGICAL TESTS

Once the initial format and content of the test have been selected, the next objective is to standardize the test, i.e., to assure "uniformity of procedure in administering and scoring the test" (40). Several practical issues must be addressed.

Test content and format

The final version of the test may not be determined until pre-testing has established the best possible form and content, as discussed in the previous section. However, if the preliminary data are to be meaningfully examined, it is important that all testers are administering the test in exactly the same manner regardless of the stage of the project. To ensure this, each step should be documented in detail in an Operations Manual which is revised as modifications are made. Depending on the level of education and experience of the field staff, the manual should be extremely explicit, providing a virtual "script" for test administration to maximize inter-rater reliability. Deviation from the script should be discouraged.

Instructions to subjects

Instructions to be given to subjects during testing should be carefully developed and standardized. Uneducated subjects who have never been subjected to test-taking situations may not understand the importance of listening attentively to instructions and following them exactly. Thus they may misunderstand the task, or give vague responses or answers which, though socially ap-

propriate, are unscorable. With such populations it is better to assume that the task is novel and provide concrete and explicit instructions. This should be followed by examples which are not scored but allow the tester to determine whether the subject has understood the task, before the actual test is given.

With a population of largely illiterate rural elderly subjects in India, we have found it useful to begin the testing session with polite conversation, followed by a "dummy test" which is not scored. The dummy test serves to get the subject into test "set" or "mood", helping him/her to comprehend that this is a new type of social situation where specific choices must be made and precise answers given. The dummy test should be or appear to be a real test, but one with a high probability of correct responses to provide the subject with early success and allay initial anxiety. In addition, we have developed various cueing devices to help subjects orient themselves to specific tasks. These will be described in a subsequent article. All such instructions, as they are developed through pre-testing, should be documented in the Operations Manual.

Instructions given to the tester

These should cover the manner and rate of test administration, timing, verbal and nonverbal communication, allowable prompting, repetition, encouragement, clarification, etc. Such details should also be documented in the Operations Manual which should be revised and updated on an ongoing basis, and used for training and retraining of field staff (testers). If the project requires translation of the tests into a different language, field staff should obviously be fluent in the language of the target population. It may be necessary for the Operations Manual to be written in this language as well.

However, a certain amount of judgement will have to be exercised by field staff in individual situations. This will improve with experience, but initially it must be developed through extensive training, role-playing, and supervision by a skilled clinician, preferably a neuropsychologist.

Since subjects will probably be anxious and somewhat bewildered by the prospect of being tested, testers must specifically be taught to be patient and provide courteous reassurance rather than provoke further anxiety. Field staff may acquire elevated social status in the community and should be firmly cautioned against appearing arrogant or domineering. Their objective should be to coax the best possible test performance from each subject without deviating from the prescribed format or providing unauthorized "help".

Test scoring

Each test should be scored in a manner which is valid, internally consistent, and allows a reasonable range of scores to emerge in the population. For tests with simple right-or-wrong answers, scoring can appear easy. Subjects, however, may provide unexpected responses, and require further clarification or prompting to elicit a scorable response. As many examples as possible of unusual responses, appropriate scores, and allowable clarifications should be included in the Operations Manual. Some cognitive functions can only be tested in a manner which requires some judgement on the part of the scorer; a particularly difficult example in illiterate populations is constructional praxis which is tested by asking the subject to draw a picture (e.g., a face) and/or copy a figure. Individuals who have never used a pen or pencil may balk at this task altogether, or make an attempt but produce a drawing which would be unacceptable from literate individuals. Alternatives to handling this problem include eliminating the task altogether; simplifying the drawing; or modifying the scoring. The latter could include making the scoring criteria more lenient, and/or developing a reliable method of giving partial credit to provide a wider range of scores. Both these modified scoring schemes would be greatly facilitated by providing the scorer with several prototype examples of correct (acceptable) and incorrect drawings; ideally, these should come from the same or a similar population. Alternatively, scoring of responses which require more clinical judgement than can be expected of lay testers could be deferred; field staff can administer the test, but bring the drawings back for scoring by the expert clinician.

Norms and standardization samples

Realistic scoring requires prior knowledge of norms against which an individual's performance

will be compared. If unavailable, norms must be established by administering the tests to a sufficiently large representative sample from the population which is ultimately to be screened for dementia. The performance of this group, known as the "standardization sample" (40), helps to establish the normal levels of performance of this community on these tests. This process, while time-consuming and labour-intensive, is clearly critical before major cross-cultural/national comparisons between diverse populations can be begun. Such comparisons will not be meaningful if the same tests are applied in the same way to two populations, one of whom produces "normal" scores which are in the "demented" range for the other.

Final diagnosis: the "Gold standard"

While a screening scale or battery provides useful information about the cognitive functioning of both the individual and the population, its primary purpose is to identify as many as possible of the cognitively impaired, potentially demented individuals in the community. Individuals classified as screen-positive, i.e., those whose test performance falls below the cutpoint selected for that population, are referred for the second stage of the evaluation: the diagnostic assessment by an expert clinician to determine whether or not dementia is present. Since the screening instrument is unlikely to have perfect sensitivity, it is desirable to estimate its "false negative" rate. This may be accomplished by also referring a random sample (possibly stratified by cognitive test scores) of screen-negative individuals for the diagnostic assessment.

The diagnostic assessment for dementia includes working up a detailed history from the subject and a reliable informant, review of medical charts, general physical examination, neuropsychiatric examination, and additional neuropsychological testing. It is also useful at this time to obtain a family history and assess exposure to potential risk factors. Using all these data, the clinician makes the final diagnosis as to the presence or absence of dementia. It is important to remember that this is a clinical/behavioral diagnosis based solely on the history and examination. The diagnostic criteria used most widely for dementia are the DSM-III-R (25) and the ICD-10 (41) criteria. The Clinical Dementia Rating Scale (42) or some other reliable measure of severity/stage of dementia should also be applied.

If a diagnosis of dementia is made, the next step is to ascertain the probable etiology of dementia. In general, the process consists of examining the manifestations and course of the dementing condition, and searching for the known causes of secondary dementia. The most commonly used diagnostic criteria for AD are the NINCDS-ADRDA criteria (43). The NINDS-AIREN (44) criteria for vascular dementia are being utilized increasingly. The NINCDS-ADRDA criteria have shown high reliability across cross-national sites (45).

While some clues may emerge in the history-taking and examination process, the differential diagnosis of dementia usually requires certain laboratory tests (basic hematological and metabolic screens, thyroid functions, Vitamin B_{12} levels, syphilis serology; neuroimaging such as CT or MRI scan of the head) to be performed. Whether these investigations should or can be pursued depends partly on the goals of the study and partly on the resources available to the study and the individual subjects/patients. In some circumstances, it may be considered necessary to order laboratory tests to follow up suspicious findings on history and examination; in others, it may be possible to carry out the full "dementia workup", including neuroimaging, on all subjects; in still others, no tests may be available. If blood is being drawn, and banking facilities are available, it is recommended that a small aliquot be stored for future research, e.g., into potential biomarkers of Alzheimer's disease, since these are less likely to be influenced by "cultural" variables and would obtain important validation from cross-national studies.

The diagnostic process should allow more flexibility than the screening process, commensurate with the expertise and judgement of the diagnostician, to allow the incorporation of all relevant data (which may vary in amount and quality among subjects) into the diagnosis. However, it should also follow a standardized protocol, allow the application of known operational diagnostic criteria, and be of demonstrated inter-rater reliability among clinicians and sites involved in the study (46). Ideally, such reliability should be formally tested by having the clini-

cians either examine the same subjects/patients, or review videotapes or paper protocols produced by one another, to determine their level of agreement and resolve discrepancies. If possible, the final diagnosis on each subject should be made by consensus among a group of experienced clinicians independently or jointly evaluating all relevant data. Maximum variability in inter-rater reliability in cross-cultural/national studies has been found in mild/early dementia, as compared to moderate and severe cases. This remains a difficult issue to resolve (47).

The clinician's diagnostic assessment is the "gold standard" against which the sensitivity and specificity of the screening instrument are judged. It is therefore a part of the standardization process of the screening instrument. By screening and "diagnosing" all subjects in the standardization sample, sensitivity and specificity of the screening tests can be calculated and compared at several potential cutpoints, allowing comparisons among the various cross-cultural/national groups, as well as the selection of the optimal cutpoint for the given population. This cutpoint would then classify subjects in the final survey into cognitively "impaired" (screen-positive) and "unimpaired" (screen-negative) groups, with only the impaired group and, if desired, a sample of "unimpaired" controls, being subjected to diagnostic assessment. The standardization of the screening and diagnostic protocols, and the selection of optimal cutpoints, are the final step in the development of the methodology for the cross-cultural/national epidemiological study.

UNEDUCATED/ILLITERATE POPULATIONS: SPECIAL CONSIDERATIONS

Relationship of education with dementia

A growing body of epidemiological literature suggests that lower levels of education are associated with a higher prevalence of dementia and that lack of education may be a risk factor for AD (6, 8, 29, 48-53), although this association was not found in other studies (54, 55). These findings must be interpreted with the greatest caution; it is critical to determine whether they reflect differences in incidence, survival, or both. If there is a genuine difference in risk, one would expect to find higher prevalence rates of AD in societies with lower educational levels, perhaps in pandemic proportions in subgroups with zero education. The question remains whether low or no education: (a) merely limits scores on the tests which are used to screen for the effects of dementing disorders; (b) is a marker of low premorbid levels of intellectual functioning; (c) diminishes "brain reserve" leading to earlier manifestation of the effects of dementia (56); or (d) is a marker of low socioeconomic status, thus serving as a surrogate for other deprivations causing the actual neuronal loss characteristic of the dementing disorders. While these hypotheses render the study of uneducated societies highly desirable, they also magnify the methodological challenge of developing appropriate cognitive tests for uneducated and illiterate populations.

The approach our group has adopted for cognitive screening of a largely illiterate elderly population in India will be reported in greater detail in a subsequent article. In brief, we have generally modified test items that require reading or writing to allow for oral presentation and response. In doing so, we have assumed that literacy is a skill developed through education and not a marker for the adequacy of the basic cognitive domain. We recognize that, in taking this approach we will not be able to detect a cognitive impairment that manifests itself solely as an acquired dyslexia, but we believe that such situations would be rare. In most cases, we believe that the primary purpose of tasks that involve reading (e.g., the Word List task mentioned earlier) is to assess some other cognitive domain (in this case, learning and memory) rather than literacy. In such situations, we believe we have gained more by including a task that is still analogous in important respects than we have lost by modifying the method of presentation. The alternative, deleting the test from the battery, would have unduly hampered our ability to detect memory impairment, the main object of the exercise.

Another challenge to the cognitive screening of uneducated individuals is the level of abstract thinking required for many tests. This factor may appear obvious when abstraction itself is being tested, e.g., with proverb interpretation for which locally familiar sayings should be selected, or recognition of similarities and differences sub-

stituted. However, abstract thinking is also required for mental arithmetic, as in the "serial sevens" subtraction task which is one of the MMSE attention subtests (26). Individuals never previously exposed to such tasks (e.g., in school) may find this test perplexing and in fact pointless. By incorporating a serial subtraction task into a story, so that concrete, recognizable units (e.g., currency) are substituted for abstract numbers, it may be possible to tap the quantitative abilities of such persons. Elsewhere (34), we have described one such modification, in which subjects are told of an individual with a given amount of money who spent the same sum each day on bus fare; the task is to calculate how much money he had left over each day. In this context, the task appeared comprehensible and acceptable to an uneducated elderly population.

There may also be, however, other more subtle, unexpected effects of education and literacy that could affect cognition in more profound and apparently unmodifiable ways, which would require the deletion of certain tests for certain populations. In less extreme situations, it should be possible at least to partly distinguish the effects of literacy from those of culture by comparing, within one culture, subgroups with different levels of literacy and education.

MEANING OF COGNITIVE TEST SCORES IN DIFFERENT CULTURES

This problem has particularly serious consequences for dementia epidemiology. Cognitive test performance is affected not only by abnormal conditions affecting mental state (e.g., delirium and dementia) but also by demographic factors such as age, gender, education (57-59), and cultural factors including comprehensibility, acceptability, perceived relevance of test content, and familiarity with the language and with testing situations, concepts, procedures, and materials. If the presence of dementia is to be suspected (and its severity to be defined) by neuropsychological test scores, it is essential to distinguish the effects of dementia on test performance from the pre-existing and independent effects of culture, language and education. No test, therefore, is completely "culture-free", at best, it can be relatively "culture-fair", i.e., it can avoid systematically penalizing members of one culture for poor performance on tests designed for, and standardized on, members of another culture. The possible confounding of "culture" by education must also be recognized. Even after translation and standardization of a "culture-fair" test, a specific score may vary considerably in clinical meaning (i.e., in its reflection of a specific level of brain impairment) from group to group, implying that tests must be independently calibrated for each group (39).

Thus, an at least partly empirical, rather than purely intuitive, approach is needed for cross-cultural test development, taking into account the many culturally determined sources of variation mentioned above. Rather than concentrating on superficial similarity of method, the challenge is to identify the important underlying dimensions on which populations are to be compared and to find ways of assessing them, which should be appropriate to the groups being compared.

CONCLUSION

Cross-cultural/national studies of the epidemiology of dementia are likely to generate significant new information about the distribution of and risk factors for the dementing disorders. Such studies are also likely to pose major logistic and methodological challenges when comparisons are to be made between developed and developing countries, and particularly when uneducated/illiterate elderly are to be studied. A prior investment in sound methodology, including creative but systematic development, pre- and pilot-testing, and standardization of cognitive screening instruments, will yield major dividends in the usefulness of such studies.

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