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EDITORIAL

Research and Alzheimer's disease: an epidemiological perspective[1]

Dementia and Alzheimer's disease attract much attention worldwide, not least because of the enormous public health implications of ageing populations in both developed and developing countries. Research in this area has become prolific, with a high profile and high technology. This has generally emphasized the disease nature of Alzheimer's disease and the dementing processes, distinguishing these from changes observed in normal ageing. However, the reason for research funding is firmly grounded in governments' concerns about the impact of future ageing populations, how these are to be tackled and planned for. An epidemiological interpretation of current research and its value to the population is, therefore, essential.

Alzheimer's disease cannot be examined in isolation from other types of dementia, since a diagnosis of dementia must always be made first and the diagnosis of Alzheimer's disease remains one of exclusion. Case definition of dementia in epidemiological studies is fraught with difficulties. Rates are calculated according to diagnosis based upon clinical impression (e.g. Parsons, 1964), computer diagnosis (Copeland *et al.* 1986*a*; Plugge *et al.* 1990), consensus diagnosis (Rocca *et al.* 1990) and the fulfilment by clinicians of formal diagnostic criteria (Bickel & Cooper, 1989; O'Connor *et al.* 1989). While computer diagnosis and fulfilment of diagnostic criteria are more standardized than other methods, variation can still occur in how criteria are fulfilled, how questions are administered and how they are coded. Computerized diagnostic algorithms must be carefully developed to avoid nonsense values, for instance a severely demented person emerging as normal because of missing values. If an algorithm relies heavily on observation it will be only as reliable as the subjective assessment it replaces. If it depends too much on interview information such as cognitive performance, missing values or culturally inappropriate cut-points may introduce bias.

The standard diagnosis against which to compare the performance of a screening test or computerized algorithm varies from study to study. Despite criticism that clinical diagnosis is not reliable, this is the standard which has been used most widely (Copeland *et al.* 1986*a*; Morgan *et al.* 1987). It could be argued, however, that this is somewhat circular and that it might be more logical to monitor progression in order to confirm diagnosis. The cases of dementia would at least remain stable, if not progress. Without frequent follow-up, not necessarily tolerated well in community studies, this may be difficult to establish, since it has been repeatedly shown that the demented are at high risk of death (Eagles *et al.* 1990; O'Connor *et al.* 1990; Evans *et al.* 1991). It cannot be assumed, however, that death before follow-up confirms diagnosis or indicates progression. The computerized algorithm of AGECAT of the Geriatric Mental State at the O3 organicity level appears to provide a moderately stable diagnosis, with 50% of 12 survivors being at the same or greater level of organicity on follow-up at, on average, 1 year 23 weeks later (Copeland *et al.* 1986*b*). In total, 97% of CAMDEX diagnoses of mild and more severe dementia were confirmed in 137 survivors at one-year follow-up in the Hughes Hall Project for Later Life (O'Connor *et al.* 1989, 1990). Ideally, in such studies, the second interview should be conducted blind to the results of the first, but this has not always been the case.

The type of patients given the diagnosis of Alzheimer's disease will depend on how vigorously other possible causes of dementia are pursued. Community studies cannot investigate cases of dementia with the same zeal as clinical studies and multi-stage sampling with intensive investigation

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of a small subgroup leads to high drop out rates. Few studies, therefore, have carried out exhaustive investigations. A community study which includes clinical examination but no investigation is likely to misdiagnose conditions such as hypothyroidism and focal lesions might be diagnosed as vascular dementia. Dementia related to Parkinson's disease would, however, be diagnosed. Conversely, a study with venepuncture but no clinical examination might diagnose hypothyroidism but miss Parkinson's disease. Where neuroimaging is available a diagnosis of vascular dementia may be more likely than where it is not. Leukoaraiosis has been found to reflect neuropathology (Janota *et al.* 1989) and this is bound to cause further confusion in differential diagnosis in the elderly where such lesions are common (Rezek *et al.* 1987). The recognition of the possible importance of new types of dementia, such as prion-related dementia (Collinge *et al.* 1990; Brown *et al.* 1991; Harrison & Roberts, 1991), diffuse Lewy body disease (Lennox *et al.* 1989) and the rediscovered frontal dementias (Hodges, 1992) further complicates the process of differential diagnosis. For many clinical studies the diagnosis of Alzheimer's disease has become more stringent with the wide adoption of the NINCDS-ADRDA criteria (McKhann *et al.* 1985). The probability of accurate identification within this group is high when compared with post-mortem appearances (Morris *et al.* 1988*a*; Burns *et al.* 1990). The Consortium to Establish a Registry for Alzheimer's Disease is an important step forward in standardized assessment of clinically identified cases (Morris *et al.* 1988*b*).

The reference standard for differential diagnosis is held to be post mortem examination of the brain since, as yet, there are no *in vivo* tests which are specific to the most common disorders. The neuropathological examination of the brain might be expected to provide a 'gold' standard, but, unfortunately, even here there are problems. Set criteria for Alzheimer's disease or vascular dementia remain contentious despite the introduction of tentative criteria in the early studies in the sixties (Byrne *et al.* 1991). It has been shown that neuropathologists vary widely in their methods and criteria (Wisniewski *et al.* 1988). Moreover, they have not always been blind to the clinical diagnosis. The pathological features held to be diagnostic of Alzheimer's disease, and to some extent vascular dementia, are found in non-demented populations (Crystal *et al.* 1988). Even within the demented group the features found in brains from subjects of different ages vary. Those who are very old and demented appear to have less of the pathognomonic features at autopsy than the young and demented (Ehrlich & Davis, 1980). Finally, the post mortem findings of Alzheimer's disease do not always agree with the known clinical findings (Terry *et al.* 1988). Thus, both in life and death, the case definition of dementia and Alzheimer's disease presents difficulties, to the extent that its very existence has been questioned (Whalley, 1987).

Epidemiological studies must be interpreted with these issues in mind. The variation in the methodology of epidemiological studies of dementia has been well reviewed recently (Kay, 1991). A comprehensive overview of European studies, in particular those that are more comparable, including prevalence, incidence and risk factors, has been carried out as part of the European Economic Community Concerted Action on the Prevention of Dementia (EURODEM – Hofman *et al.* 1991; Launer, 1992).

Prevalence is a function of incidence and survival and is affected by migration, and, if studies are carried out in the community only, by institutionalization. Prevalence studies have been carried out worldwide, using a variety of sampling and screening methods and case definitions. These report widely differing refusal rates. All these may have led to differences observed between studies such as low rates with the use of short cognitive scales (for example in Melton Mowbray – Clarke *et al.* 1984) which are known to be insensitive to mild dementia, although accurate for moderate to severe dementia (Kay *et al.* 1990; Brayne & Calloway, 1990; Clarke *et al.* 1991).

A meta-analysis of worldwide prevalence studies of dementia revealed that, although rates varied, the effect of age on ratios was consistent with doubling every 5·1 years (Jorm *et al.* 1987). A separate, but similar and more recent, exercise has been carried out on recent European studies. Of 23 studies, only 12 had sufficiently similar methodology to carry out a combined analysis. The rates of best fit for the worldwide figures of Jorm for moderate and severe dementia were very similar to the overall rates arrived at in the European study for all levels of dementia. The rates were as follows, with

Jorm's modelled figures (%) in parentheses: 60–64 1·0 (0·7), 65–69 1·4 (1·4), 70–74 4·1 (2·8), 75–79 5·7 (5·6), 80–85 13·0 (10·5), 85–89 21·6 (20·8), 90–94 32·2 (38·6) (Jorm *et al.* 1987; Hofman *et al.* 1991). The similarity of the rates is partly because some studies were included in both exercises. There were no significant differences between men and women, but more of the dementias in men appeared to be vascular or secondary to other conditions such as alcohol abuse. Rural populations may demonstrate lower rates for more severe levels of dementia, but very few such studies have been carried out (Brayne & Calloway, 1989).

Unfortunately, it is not possible to comment on secular trends because of these methodological differences, but there is no suggestion of an increase in prevalence. If anything, decreases have been suggested based on the figures reported from Newcastle, Melton Mowbray and Cambridge (Kay *et al.* 1968; Clarke *et al.* 1984; O'Connor *et al.* 1989).

In the EURODEM exercise there were five studies which attempted differential diagnosis. There was variation in the way in which other diagnoses were excluded, and all the studies were conducted before the recent interest in diffuse Lewy body disease and frontal dementias. The overall mean rates (%) for Alzheimer's disease were as follows: both sexes 30–59 0·02, 60–69 0·3, 70–79 3·1, 80–89 10·8; men 30–59 0, 60–69 0·3, 70–79 2·5, 80–89 10·0; women 30–59 0·03; 60–69 0·4, 70–79 3·6, 80–89 11·2. Alzheimer's disease accounted for the majority of the dementias in most, if not all, of the studies. The rates increased exponentially with age and were similar, although in some populations the rates for women were higher than those for men (Rocca *et al.* 1991*b*). These results contrast with a study from the United States where the rates for Alzheimer's disease in a community sample from Boston were very much higher (Evans, D. A. *et al.* 1989). Methodological issues may account for this high rate, including an emphasis on psychometric tests for the diagnosis in a population with low levels of education. In addition, the effect of migration and loss of cultural environment, in particular contact with first language, on performance on cognitive scales is poorly understood. The exercise for vascular dementia by EURODEM arrived at more variable results, with less of a rise with age than Alzheimer's disease, and rates for women lower than men (Rocca *et al.* 1991*c*).

Survival is known to be shorter than expected for Alzheimer's disease (Evans *et al.* 1991). The survival of people with any degree of cognitive impairment or actual diagnoses of dementia has been consistently reported as inversely related to degree of impairment, unrelated to social class, physical disability or impairment in activities of daily living (Jagger *et al.* 1989). Although an increase in survival may be apparent in hospital samples, it has not been found in the long-term studies at the Mayo Clinic (Kokmen *et al.* 1990).

Incidence studies are of more value for comparing populations. Incidence studies based on the identification of new cases in services have led to low incidence estimates. Field incidence studies are difficult and expensive; consequently, few have been carried out and these tend to provide rates of all dementias rather than Alzheimer's disease. As with prevalence studies there are similarities in reported rates, with marked rises with age. No secular tends have been found as yet (Kokmen *et al.* 1990). There are too few incidence studies with such diverse methods that combined analysis is not possible. However, many studies are under way or being planned which have a core protocol developed within the EURODEM group (Launer, 1992). Recent follow-up studies of non-demented cohorts (Bordeaux, Dartigues *et al.* 1992; Cambridge, Brayne *et al.* 1992; Liverpool, Copeland *et al.* 1992; Nottingham, Morgan *et al.* 1992) suggest rates in the region of 1·4% per annum for the 65 and over age group, and 3·4% per annum for the 75 and over age group (Kay, 1991; Launer, 1992). These are sequential cross-sectional studies of cohorts and so selective migration into institutions and loss due to death, refusal and other migration can bias results downwards, as it is known that death and refusal are related to cognitive impairment and dementia (Livingston *et al.* 1990). Adjustment for these losses can be made but only if there is enough information on the types of people who are lost with enough data points on similar groups. For comparison of incidence rates different success of follow-up and methods of correction could therefore further hamper comparison.

There are relatively few studies of cognition in ageing populations which are truly population based. There are some exceptions such as the Gothenburg study (Berg, 1980). Incidence rates for

dementia from these studies will be available in the future, but it appears that there are relatively few predictors of cognitive decline. There are none for Alzheimer's disease specifically. Twin cohorts have been reported as showing differential rates of dementia for those with initial poor cognitive performance (Jarvik *et al.* 1980). If the diagnostic criteria are heavily dependent on level cognitive function this finding may be an artefact of measurement methods. Predictors of cognitive decline from volunteer cohorts, such as the Duke Longitudinal Study and the Bronx Aging Study (Crystal *et al.* 1988) have been given as lower respiratory function, high blood pressure, low social class, inactivity, hearing impairment and low frequency of bowel movements (Henderson, 1988). The information collected at baseline by such longitudinal studies varies considerably, as they were initially designed for different purposes. It is encouraging that several well-established cohort studies designed to examine risk for coronary heart disease, such as the Caerphilly study (Elwood *et al.* 1991) and the Whitehall civil servant studies (Marmot *et al.* 1991), are now assessing cognitive function. These studies will be able to examine change in cognitive function in relation to vascular risk factors and actual vascular pathologies measured in mid-life, thus avoiding the circularity of the case control method in vascular dementia, where the diagnostic criteria preclude the examination of some risk factors. Other groups are following cohorts of stroke patients, which should help clarify the relation of position, numbers and size of lesions with cognitive impairment evaluated longitudinally (Tatemichi *et al.* 1990).

With an incidence rate of all dementias of 1–2% in the 65 and over age group, the use of cohort methods to identify risk factors is fraught with difficulty. Few risk factors have therefore been identified by this method. It has been suggested that workers exposed to solvents have higher rates of dementia (Axelsson *et al.* 1976), but this has not been confirmed as yet. The most important association at present is that with aluminium (Martyn & Candy, 1991). One retrospective study of miners exposed to aluminium dust reported a significant relationship of cognitive function with levels of exposure (Rifet *et al.* 1991). Others have reported a relationship of either rates of dementia or degree of cognitive impairment with aluminium in the water supply, which may be the most bioavailable form of aluminium (Martyn *et al.* 1989; Michel *et al.* 1991; Neri & Hewitt 1991). There are considerable difficulties with the interpretation of these findings, as all the measures are indirect. Aluminium has a complex pathway in the human body and more is ingested in food than water. Levels of cognitive function do not necessarily reflect decline, but can reflect education and cultural background. Confounding has, therefore, not been ruled out, that is an association not between aluminium exposure and cognitive decline, but of both to a third factor. If there really is a relationship between aluminium and Alzheimer's disease it is surprising that the population studies so far conducted in Europe in countries with different exposure patterns, such as in tea drinking (tea is high in aluminium), have not identified wide variations in rates. The role of free radicals, implicated in ageing, malignancy, heart disease and now Alzheimer's disease, in the aluminium hypothesis has yet to be investigated *in vivo* (Evans, P.H. *et al.* 1989; Volicer & Crino, 1990). Further investigation is essential (Cooper, 1991).

Because the incidence of Alzheimer's disease is low, case–control methods have been used to examine risk. Many case–control studies have now been carried out to examine differences in putative risk factors in cases of Alzheimer's disease and controls. However, they have been flawed by their bias in selection of cases and controls. Few are population based, and most are based on prevalent, not incident, cases and can therefore be biased by factors related to survival. Information about exposure must be collected from an informant for both the case and the control, introducing further biases (Kupper, 1984; Clayton, 1991). Several of the consistent findings, such as a single significant head injury in earlier life, could be accounted for by this bias. A more recent finding of a negative association with smoking (van Duijn & Hofman, 1990; Graves *et al.* 1991*a*) is of interest because of the relationship of nicotinic receptors to smoking and to Alzheimer's disease. The relationship could be accounted for by the relationship of smoking with survival, thereby creating an apparent protective effect (Brayne, 1991). Similar difficulties with the interpretation of associations have been noted before, for example in the association of certain infections with leukaemia (Hennekens & Buring, 1987). Not all studies have reported the same association, some

the reverse (Shalat *et al.* 1987). In favour of this association is the earlier onset of disease in non-smokers than in smokers in concordant twins (van Duijn & Hofman, 1990; van Duijn, 1992).

Diagnostic criteria usually exclude cases of dementia possibly secondary to vascular events, alcohol and hypothyroidism (as well as other medical conditions). Several studies have gone on to look at these factors as possible risk factors, despite the fact that the selection method precludes the possibility of examining them in an unbiased manner.

A recent combined re-analysis of case–control studies of Alzheimer's disease (van Duijn *et al.* 1991*a*), where methodologies were reasonably similar has again shown the key associations: family history of dementia (Odds ratio 3·5), Parkinson's disease (2·4), and Down's syndrome (2·7), maternal age at birth (1·7 at over 40 years), head trauma (1·82), hypothyroidism (2·3) and depression more than 10 years before onset of dementia (1·92). Negative associations were arthritis (0·7), headaches (0·7) and blood transfusions (0·6). These latter associations only just reach significance at the 0·05 level (Breteler *et al.* 1991; Graves *et al.* 1991*a*, *b*; Jorm *et al.* 1991; Mortimer *et al.* 1991; Rocca *et al.* 1991*a*; van Duijn *et al.* 1991*b*). Some of the associations such as head injury are stronger in sporadic than in familial cases, arguing for multiple aetiological influences and a separation of sporadic and familial in analysis (Rocca & Amaducci, 1989). Despite the increased power of these studies (i.e. the ability to detect a true effect) the possible biases remain the same (Davey Smith & Philips, 1990).

A further consideration of such studies is the implication of findings for the population. Odds ratios estimate relative risk which measures the ratio of incidence of a disorder in an exposed and non-exposed group. This measure is important in the understanding of aetiology. Attributable risk, population attributable risk and population excess risk are of more importance to the community, giving an idea of how important a given risk factor is in a particular population. This is well illustrated by the possible association with head injury. Head injury is undesirable for short-term reasons, but as a risk for dementia the attributable risk depends on how many people are exposed who then go on to develop dementia as a proportion of all those who develop dementia. Despite the odds ratio of 2·7 for head trauma in males (Mortimer *et al.* 1991), only 3% of all Alzheimer's disease cases might be attributable to this, because a variable, but small proportion, such as 5% of the elderly population, has experienced sufficiently serious head injury. Thus, the potential for public health measures based on the risks identified so far are limited (Brayne, 1991). The population excess risk of aluminium exposure in the water supply is of much greater importance despite lower odds ratios, if proven, since large sections of the population are exposed.

Different populations may have very different patterns of dementia. Intriguing findings have been reported from studies comparing Cree Indians with Whites in Indiana, with the finding that the Cree have more secondary dementias and less Alzheimer's disease (Hendrie, personal communication). A study of an elderly population in Nigeria found no demented individuals although several had cognitive impairment (Osuntokun *et al.* 1990). In the United States several studies have found that Blacks have higher rates of apparent dementia than Whites, and it has been suggested that this may be due to secondary dementias (Fillenbaum *et al.* 1988). Once accurate diagnosis can be made, such cross-cultural studies are likely to become of even greater importance in the search for the determinants of different pathologies. These studies present challenges in the search for appropriate measures, both screening and diagnostic, that can be applied with equal validity in different settings (Fuld *et al.* 1988; Li *et al.* 1989).

Researchers in the field of molecular biology are seeking fundamental lesions, including single faulty genes for Alzheimer's disease. It is by no means clear which of the classical lesions associated with Alzheimer's disease cause the decline noted during life. The recent findings of a point mutation on chromosome 21 in a single pedigree have roused great interest (Goate *et al.* 1991). However, examination of brain tissue from one of this pedigree showed atypical pathology, including Lewy bodies (Rosser, personal communication). The importance of such findings is likely to be that they will help to elucidate mechanisms more clearly (Hardy, 1991). Not all Alzheimer's disease is familial, and only a handful of the known pedigrees in the world are accounted for by the mutation found in this study (Naruse *et al.* 1991). A community based study in Holland found none out of 197 cases

to be associated with this mutation (van Duijn *et al.* 1991*c*; van Duijn, 1992). Other advances in molecular biology, such as the elucidation of the structure of tau and beta amyloid and the relation between these two have not as yet helped the search for causation, but continue to make clearer the pathological expression and possible therapeutic strategies for Alzheimer's disease (Selkoe, 1989; Harrington *et al.* 1991).

In public health terms the predominance of Alzheimer's disease in most Western countries has important implications. Other dementias, such as vascular dementias, appear at present to be more amenable to prevention or intervention. Stroke is predictive of vascular dementia (Tatemichi *et al.* 1990), and predictors of stroke are hypertension, myocardial infarction, smoking and alcohol (Himmelman *et al.* 1988; Shaper *et al.* 1991). Effective measures against some of these may reduce the incidence, or progression, of vascular dementia. In some populations public health measures already appear to be influencing ischaemic heart disease risk factors (Sigfusson *et al.* 1991). Addressing other observed health inequalities in the population such as respiratory disease (Marmot *et al.* 1991) may also be beneficial in the future, particularly in men. Women, however, form the largest part of the very elderly and it is in these groups that substantial increases in the population are expected.

The value of the categorical model of mental disorders in aetiological research has been questioned (Rose, 1989), and in particular for dementia (Jorm & Henderson 1985; Brayne & Calloway, 1988). In the 1960s this debate centred on hypertension – 'Medicine in its present state can count up to two but not beyond' (Pickering, 1968). Given the difficulties of diagnosis, differential diagnosis and the interface between normality and abnormality, it is perhaps time to move on and change the model on which we base research. Case definition is essential for operational decisions but too inefficient to be a priority in research (Rose, 1989). In epidemiological studies this is an important issue. In a longitudinal study at what point is the person an incident case of dementia? In terms of the diagnostic criteria for ICD-10 it is six months after the point at which those around the person perceive a failure in social and behavioural functioning. This creates an apparent threshold which may vary between social groups even when standardized diagnostic criteria are applied, and within social groups according to the age and health of the individual and sociocultural expectations of ageing. The criteria for Alzheimer's disease also stipulate gradual deterioration. Since the core criterion for dementia is cognitive decline, at least for CAMDEX and ICD-10, a model based on repeated measurement with tracking of cognitive function in parallel with behavioural function and activities of daily living may be more informative. This would enable comparison of rates of change. These are not mutually exclusive approaches since the continuous model allows fuller use of the data which must in any case be collected.

What then is the ideal research programme to address these fundamental issues? We need to explore a continuous model where change over time is documented in populations, with follow-up at more than two time points, to examine rates of decline. These could then be correlated with the pathologies found at post-mortem. Detailed testing during life, and examination at death, would allow global, regional and lesion specific correlations to be computed. Thus we may begin to understand the significance of lesions such as plaques and tangles, Lewy bodies, neuronal loss, synapse loss and dendritic sprouting, prion positivity, and vascular lesions for the decline noted in normal ageing and the pathological decline of the demented. It may be that absence of lesions is associated with good maintenance of function (successful ageing) and that a small collection of one or more lesions is associated with some decline (usual ageing) and that many lesions are associated with pathological decline (Rowe & Kahn, 1987). Thus, risks could be examined in relation to rate of decline rather than presence or absence of a disease type. Similarly, such a study could provide a greater understanding of the relationship of systemic illness and medical history to cognitive decline (Holland & Rabbitt, 1991; Houx *et al.* 1991). The relationship between the biological processes occurring with ageing and the emergence of Alzheimer's disease would also be clarified (Bird *et al.* 1989).

The longitudinal component is essential, since cross sectional studies may lead to paradoxical results. Potential risk factors must be measured at the outset in order to avoid biased collection of

information after dementia has occurred, and to examine the relationship of the risk factor itself to survival. Clinicopathological studies in cross-sectional groups can also appear paradoxical, so that someone with normal levels of cognitive function shortly before death may have many lesions, but may have declined considerably from an earlier even higher level of functioning. A high level of cooperation from the community is essential, with a statements of intent to donate tissue post mortem obtained in advance from the individual and their families in groups representing the full range of function (Beardsall *et al.* 1992). This requires considerable resources, including liaison nurses.

Comparison of such studies across cultures will begin to resolve the issue of sociocultural variation in the perception and diagnosis of dementia and its underlying pathologies. In the absence of easily testable hypotheses about the nature of Alzheimer's disease and the causation of this and other dementias it would seem that we have to embark upon this labour intensive approach to come closer to prevention in the future. If it is found that a continuous model is more appropriate to the dementias than a disease model, preventive strategies may have implications for the normal ageing population. 'So long as attention is confined to conspicuous cases, the underlying causes of incidence and the means of controlling them will continue to evade attention' (Rose, 1981).

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