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CHAPTER 8

The Epidemiology of Dementia and Alzheimer Disease

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Our understanding of the epidemiology of Alzheimer disease (AD) has advanced rapidly during the past decade. Community (population) studies in many countries have confirmed that the prevalence of AD (and of vascular dementia) rises in an approximately exponential fashion at least between ages 65 and 85, doubling with every 5 years of age; comparison of population studies between different countries has shown age-specific prevalence rates to be similar *within a factor of two* among countries as diverse as China, Japan, Great Britain, France, Italy, and the United States. From these population studies other demographic factors, including gender (women may be more susceptible to AD than men), poor education, and perhaps certain occupations have emerged as important putative risk factors. Moreover, case–control and longitudinal studies have confirmed the importance of family history as a major risk factor, and other, somewhat unexpected risk factors, such as head trauma and coronary artery disease, have been identified. From these findings, together with current knowledge of molecular, genetic, and pathological features of AD, a picture emerges of the interaction over time of these risk factors with the biological factors that lead to the development of the Alzheimer process.

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CASE IDENTIFICATION: CRITERIA FOR THE DIAGNOSIS OF DEMENTIA AND ALZHEIMER DISEASE USED IN EPIDEMIOLOGICAL STUDIES

These epidemiological advances have resulted largely from the development in the early 1980s of a consensus on acceptable diagnostic criteria for dementia and AD. The importance of a consensus in regard to "caseness" is basic to epidemiological studies. The most widely accepted diagnostic criteria for dementia are based on the principles introduced in 1980 in the third edition of the American Psychiatric Association's *Di-*

agnostic and Statistical Manual of Mental Disorders (DSM-III) (1) and the subsequent delineation of criteria for "probable" AD by a work group established jointly by the National Institutes of Neurological and Communicative Disorders and Stroke (NINCDS) and Alzheimer's Disease and Related Disorders Association (ADRDA) (2). Before adoption of the DSM-III criteria, the diagnosis of dementia had been subject to error rates as high as 30%, in part owing to confusion of the diagnosis of dementia and depression [see, for example, Ron et al. (3)]. With the use of DSM-III criteria, the accuracy of diagnosis of the dementia syndrome has increased to over 98% in clinical series (4). Consequently, in case–control studies in which cases of AD are selected from the clinic population, the likelihood of a clinical case being AD is very high.

The accuracy of current diagnostic criteria in the clinic does not necessarily apply to community or population studies. Here the sensitivity and specificity of diagnostic criteria are likely to be the focus of intensive investigation in the next several years. In community studies the difficulty of diagnosing dementia in elderly subjects who are very ill, in those with marked hearing or visual impairments, and in some with limited education decreases the accuracy of diagnosis. Moreover, it has become evident that the conservative DSM-III and NINCDS/ADRDA criteria may result in classification of mild dementia as being questionable or normal. For example, in the Shanghai survey to be discussed below, for every two cases that met DSM-III criteria for dementia there was one case classified as "possible dementia" that did not meet DSM-III criteria; subsequent follow-up has shown that many of these subjects were indeed in the early stages of dementia and in this sense had been misclassified.

AN OVERVIEW OF ADVANCES AND QUESTIONS THAT ARISE

Despite these problems, which must be addressed during the next decade, a number of clear-cut findings have emerged, and are summarized as follows:

1. Age is the single most important risk factor for dementias of all kinds, including AD. The prevalence of dementia doubles approximately every 5 years in individuals between the ages of 65 and 85. Data on individuals below age 65 or above age 85 are insufficient to be certain whether this apparently exponential relationship holds; very likely a more complex relationship such as the logit model would be necessary to account for a broader age range. This is important as individuals over the age of 85 represent the fastest growing segment of our population and the accurate projection of future cases will depend on the correct model.

2. In most, but not all, studies, women seem to be at greater risk for dementia, and in virtually all studies women are at greater risk for AD, whereas men appear to be at somewhat greater risk for vascular dementia. If AD is indeed more common in women, this might imply an effect of hormones on the development of AD, which could have important public health and therapeutic consequences. It is also possible that some of these differences could be accounted for by secular effects such as the relative lack of education (see 3, below). Moreover, more prevalent cerebrovascular disease may lead to overdiagnosis of vascular dementia in males and hence artifactually increase the proportion of women with the clinical diagnosis of AD.

3. Lack of education is a risk factor for dementia, probably for both Alzheimer and vascular dementia. An uneducated individual over 75 is at about twice the risk for dementia as is one who has completed at least eight grades of school.

4. A history of AD in a first-degree relative—mother, father, brother, or sister—increases the risk of developing dementia approximately fourfold. Although this is certainly true over a wide range of ages, it is not clear if it holds for those over age 80.

5. Head injury, either a single episode leading to unconsciousness or hospitalization, or repeated head injuries, as in the case of boxers, is a risk factor for AD with a relative risk (RR) greater than 2. Concern that this risk factor, which has been noted fairly consistently in case–control studies, might be due to selective recall by family or friends of individuals with AD is counterbalanced by the observation that head injury often produces diffuse β-amyloid plaques in the brain, which are similar to those present in AD.

6. Intriguing preliminary data, which require verification, suggest that in the very elderly, myocardial ischemia may be a risk factor for dementia, particularly in women, again acting through the production of diffuse β-amyloid plaques.

7. Smoking has frequently been found to be a protective factor for AD in various case–control studies, but there are several uncertainties concerning this risk factor; for example, are smokers more likely to suffer strokes, so that those who develop AD are misdiagnosed as having multi-infarct dementia (MID)? If nicotine is a protective risk factor, then the capacity of this drug to up-regulate its receptors might be involved in its protective action.

8. An inconsistent but intriguing potential risk factor is maternal age. An increase in AD has been reported in some studies, but not in others, in subjects born to mothers over the age of 40 years.

9. A number of other risk factors have been reported in one or two case–control studies, but not confirmed by other studies. Some of these, such as ex-

posure to aluminum, may act as very weak risk factors.

CASE–CONTROL STUDIES OF AD

Epidemiologists recognize that case–control studies offer the most cost-efficient method of identifying risk factors. As cases and controls are usually matched in terms of age, gender, and socioeconomic characteristics, these particular demographic variables cannot be ascertained as risk factors within such studies. However, differences in coexistent diseases and in the history of various exposures can be identified. Normally, when such clues have been found, it is preferable to carry out prospective studies in which exact exposure to a risk factor can be determined more accurately to verify the findings. Regarding AD, a large number of case–control studies have now been carried out that have led to identification of interesting putative risk factors. Such case–control studies have an advantage over population studies in that subjects who unequivocally meet the criteria for dementia and probable AD are normally included as cases. Hence, the cases meet the best available clinical description of AD.

A case–control study carried out approximately 10 years ago by Heyman et al. (5) should be noted because of its superb methodological design. The AD cases were recruited from known patients and were each required to have an informant who could give a history. Similarly, the controls who were included also had an informant available so that histories for AD patients and controls were gotten from informants for both the cases and the controls. The controls were sought by random-digit dialing of the last four digits of the telephone number of each case, thus obtaining someone in the neighborhood of the case, so that an age- and gender-matched individual in the same neighborhood as the case was chosen. Some degree of socioeconomic balance was assured on the basis of this random digit dialing. As anticipated, family history was a strong risk factor. A new and striking risk factor to come out of the study was the existence of a history of head injury up to 30 years prior to the onset of AD. The odds ratio approached 6 comparing the history of head injury in cases with that in controls. Head injury was defined as one sufficient to produce unconsciousness. Another possible risk factor found was that of prior history of thyroid disease.

Similar findings of head injury as a risk factor were obtained by Mortimer et al. (6) in a case–control study involving Alzheimer patients seen at a Veterans Administration (VA) hospital. In this study, some of the instances of head injury could be verified with prior army or VA hospital charts. Subsequently, a number of case–controls studies supported the importance of head injury as a risk factor, while others found very little effect.

The EURODEM Analyses

To deal with this variation in reports of risk factors, a European group (EURODEM) brought together the principal investigators of 11 case–control studies [including those of Heyman et al. (5) and Mortimer et al. (6)] and obtained their agreement to make their data available so that combined analyses could be carried out (7). All of the studies had used DSM-III or NINCDS/ADRDA criteria. The EURODEM group selected 11 case–control studies as meeting the standards for their collaborative reanalysis. These included studies from Australia [Broe et al. (8)—170 cases]; Finland [Soininen et al. (9)—63 cases]; Italy [Amaducci et al. (10)—116 cases]; Japan [Kondo et al. (11)—34 cases]; Netherlands [Hofman et al. (12)—198 cases]; and United States—Bedford, Massachusetts [Shalat et al. (13)—106 cases], Denver [Chandra et al. (14)—64 cases], Durham, North Carolina [Heyman et al. (5)—46 cases], Minneapolis [Mortimer et al. (6)—78 cases], Rochester, Minnesota [Kokmen et al. (15)—192 cases], Seattle [Graves et al. (16)—130 cases]. Most of the cases used in the EURODEM analysis were obtained from hospitals or clinics. In various analyses, specific series had to be excluded for analysis. For example, the Bedford series excluded individuals with history of severe head trauma and could not be used for study of head injury as a risk factor. Individuals from all studies met NINCDS/ADRDA or

TABLE 1. *EURODEM case–control studies: risk factors for AD*

Variable	Cases	Controls	Odds ratio	95% CI
Family history of dementia	305/894	140/894	3.5	2.6–6.9
Family history of Parkinson disease	20/312	8/294	2.4	1.0–5.8
Head injury	87/1,059	50/1,059	1.8	1.3–2.7
Head injury in sporadic cases	31/304	14/304	2.3	1.2–4.8
Maternal age >40	47/446	28/447	1.7	1.0–2.9
Thyroid disease	110/994	115/991	1.0	0.8–1.3
Hypothyroidism	17/655	8/732	2.3	1.0–5.4
Down syndrome	20/588	7/615	2.7	1.2–5.7
Depression in late-onset (≥70) cases	41/524	18/509	2.4	1.4–4.4
Ever smoked	477/899	563/955	0.78	0.62–0.98

CI, confidence interval.

DSM-III criteria for probable dementia. Major findings from the EURODEM reanalysis are shown in Table 1.

Head Injury as a Risk Factor for AD

In regard to head injury, the seven studies pooled (N = 1,059 cases, 1,059 controls) included both those that found a strong effect (5,6,10), and those that had reported no significant effect (14,15). When pooled, a highly significant effect of head injury was found with a risk ratio of approximately 1.82 and 95% confidence intervals (CI) of 1.26 to 2.67 (17). Stratified analysis showed stronger association in cases without a positive family history of dementia (RR = 2.31) than in familial cases (RR = 1.42) and was greater for males than females, but was the same for those with onset before age 70 and those with onset after age 70. There was no interaction effect between head trauma and family history, suggesting that these factors operate independently.

Thus, the data from case–control studies are consistent enough that head injury can now be regarded as a likely risk factor for AD. In a later section we will discuss a plausible biological mechanism linking head injury and AD. Epidemiologically, however, there is always the problem of selective recall in case—control studies. Could family members, "the informants," of the cases have remembered head injuries over a period of time when they were concerned about the patient's progressive dementia, whereas the relatives of the control, or the controls themselves, would not have thought about prior head trauma and not have recalled as many instances? Certainly, such selective recall could have occurred, but the fact that head injury was found to be such an important risk factor in the very first case–control studies at a time when it was not thought to be a risk factor and the fact that other important life events that might have been selectively recalled were not consistently present among individuals with AD suggest that this is indeed a true risk factor.

Family History as a Risk Factor for AD

Next to age, the predominant risk factor for AD is that of family history, that is, the occurrence of AD in a first-degree relative (mother, father, brother, or sister). The EURODEM analysis reported by van Duijn et al. (18) utilized data from eight of the case–control studies. The overall relative risk was 3.5 (95% CI = 2.6–4.6). The relative risk was highest in those with onset at ages 60 to 69 (RR = 5.3; CI = 2.8–10), but still significant in those with onset between ages 70 and 79 (RR = 2.3; CI = 1.4–3.6) and those with onset after age 80 (RR = 2.6; CI = 1.3–5.2). In individuals who had two or more first-degree relatives, the relative risk increased to 7.5 (3.3–8.7). Surprisingly, the relative risk of AD for those with a positive family history of Parkinson disease was 2.4 (1.0–5.8), an interesting but not quite significant finding. Similarly, the association between AD and family history of Down syndrome was just significant, the relative risk of 2.7 with a 95% confidence interval of 1.2–5.7.

Does Down Syndrome Occur More Frequently in AD Families?

It has long been known that individuals with Down syndrome develop the neuropathological features of AD by age 35 (19). The inverse relationship, that is, an increase in children with Down syndrome in families in which one member has AD, was first reported by Heston (20) in 1977 and is apparently confirmed by the EURODEM study as noted above (RR = 2.7, 95% CI = 1.2–5.7) (18) although others (21,22) have not been able to demonstrate such a relationship. The obvious possibility, however, that AD subjects might have a triplication of some chromosome 21 genes has not been supported by direct analysis (23,24). Another risk factor that was sought because of the Down relationship was an effect of *advanced maternal age* reported by Cohen and Eisdorfer (25) in 1982. Almost immediately after publication of this finding, both positive and negative reports were published (5,6,22,26–29). In the EURODEM reanalysis (29) only four studies addressed this issue; these showed a relative risk of 1.7 for maternal age over 40 (29), but this was not statistically significant with a 95% confidence interval of 1.0–2.9. Hofman et al. (30) recommended further investigation of this question.

EURODEM reanalyzed a wide variety of putative risk factors that had been addressed by the constituent case–control studies. Detailed analysis of prior alcohol consumption in terms of average weekly intake failed to show any excess risk (31). In this regard, case–control studies in which NINCDS/ADRDA criteria are used are likely to fail to identify a relationship between alcoholism and AD since the diagnostic criteria for probable AD would exclude individuals with severe alcoholism who could have an alcoholic dementia. In a recent population-based case–control study from Stockholm (32) that used modified DSM-III criteria (33) for the diagnosis of AD, a strong effect of increased alcohol consumption (RR = 4.4; CI = 1.4–13.8) was found. The possibility of such a relationship needs to be investigated in prospective studies.

A disturbing finding reported both in case–control and in longitudinal studies is a possible protective ef-

fect of smoking in regard to AD. Thus in the EURODEM reanalysis, a statistically significant inverse relationship between smoking and AD "was observed at all levels of analysis, with a trend toward decreasing risk with increasing consumption ($p = .0003$)" (31, p. S48). Although this relationship might be due to an actual protective effect of nicotine (which may up-regulate acetylcholine nicotinic receptors) or to an effect of smoking on survival, another effect of smoking might be to increase the risk of strokes in AD so that misdiagnosis as vascular dementia would occur.

Thyroid disease and hypothyroidism as risk factors for AD were initially reported by Heyman et al. (5). A history of hypothyroidism was marginally significant as a risk factor in the EURODEM analysis (Table 1) (34). In regard to psychiatric history and stress, no relationship of AD to death of spouse, death of a child, or divorce was found (35). In some cases of AD, depression occurs as an early symptom, often preceding diagnosis. In the EURODEM analysis, however, depression occurring more than 10 years before AD onset, although infrequent, was a significant risk factor (RR = 2.0; CI = 1.06–3.80) (35).

In the popular press, exposure to aluminum or aluminum products has been the most feared risk factor for AD. The failure of subjects undergoing renal dialysis who ingested large amounts of aluminum antacids to develop AD would militate against the importance of ordinary aluminum exposure (36). Indeed none of the case–control studies has found a relationship of AD to aluminum antacid intake or use of aluminum cookware, although a single study reported a minimal increased risk with the use of aluminum antiperspirants (37). For an expanded discussion of aluminum in AD, see the chapter by Markesbery and Ehmann.

PREVALENCE OF DEMENTIA AND AD IN COMMUNITY STUDIES

Prevalence studies of dementia and AD provide an important tool for understanding this age-related public health problem. In recent years, multiple studies have been performed in various locations worldwide. These studies allow comparison of data obtained from different populations. Although these comparisons can be used to generate new hypotheses, care must be taken in interpreting results since study differences may reflect disparities in methodology (design or case ascertainment) or differences in study site characteristics (institutionalization or survival rates) (38) rather than actual differences in cases. The use of death certificate data for case ascertainment has not been practical as this is likely to identify only about one-quarter of the subjects suffering from dementia (39). The lack of biological markers or universally accepted criteria for what constitutes a case has posed the single greatest problem for prevalence studies of AD. Epidemiologic surveys have used a wide range of techniques for case identification. Even the use of similar strategies and instruments in different sites might not produce equivalent results owing to cultural diversity.

Case Ascertainment and Diagnostic Criteria for Dementia and AD in Community Studies

Overall, a significant part of the variation in prevalence reported in current studies is likely to be due to differences in methodology. The diagnosis of early dementia presents a particular problem in community studies and some investigators have chosen to report prevalence rates only for severe cases (40,41). In particular, the use of different criteria for diagnosing mild dementia can result in markedly different prevalence rates (42). A recent revision of DSM-III (DSM-III-R) (33), which includes some testing recommendations, may exclude a few mild cases since the tests recommended are not particularly sensitive in identifying early changes in cognition. Some authors have argued that mild cases are excluded by the DSM-III requirement that there be "loss of sufficient severity to interfere with social and/or occupational functioning." Evans et al. (43) have argued that this criterion is difficult to apply to a community study because "participants differ both with regard to the availability of family or friends and the sensitivity of these persons to manifestations of disease" (43, p. 2553). However, Hill et al. (44) found that a culturally adapted version of a functional scale developed by Pfeffer et al. (45) in southern California worked well in the Shanghai study. When the requirement for functional disability is waived, studies tend to have higher prevalence rates of dementia, but it is unclear whether the very high prevalence rates of dementia and AD (approaching 48% at age 90) in the East Boston survey (43) can be explained by the investigators' decision not to require formal evidence of functional disability.

The most frequently used criteria for the diagnosis of AD are those developed by the NINCDS–ADRDA Work Group, Task Force on AD (2). These criteria specify deficits in two or more areas of cognition. Studies [such as the Framingham study (46)] that use the criteria established by Cummings and Benson (47) that require evidence of compromise in at least three spheres of mental activity might thereby eliminate milder cases and lower the prevalence estimation. Another approach that is likely to lower the prevalence rate of dementia is the identification of cases of dementia and AD from medical records (48), because even in a medically sophisticated community it is

likely that some patients with dementia do not seek help from the physician; or, if they are being treated for other illnesses, the physician may not recognize that they have dementia.

In diagnosing dementing illnesses in the community, it is not always possible to carry out radiological and laboratory studies for economic and other reasons. Hence it is more difficult to rule out systemic or focal disorders that might present as dementia. This may lower the accuracy of the differential diagnosis of AD. The clinical differentiation of true vascular dementia from the so-called mixed cases—AD patients with a coincident stroke—has proven to be imprecise using either the Hachinski scale (49) or the Rosen et al. (50) modification alone, but Erkinjuntti et al. (51) have reported quite good clinical pathological confirmation when CT scans are also utilized to confirm the diagnosis. Thus, in the 1987 Shanghai survey, which did not include imaging procedures, the investigators chose to report age-specific prevalence rates for dementia, and have given an estimation of the percentage of such cases likely to be secondary to AD based on the clinician's examination (52).

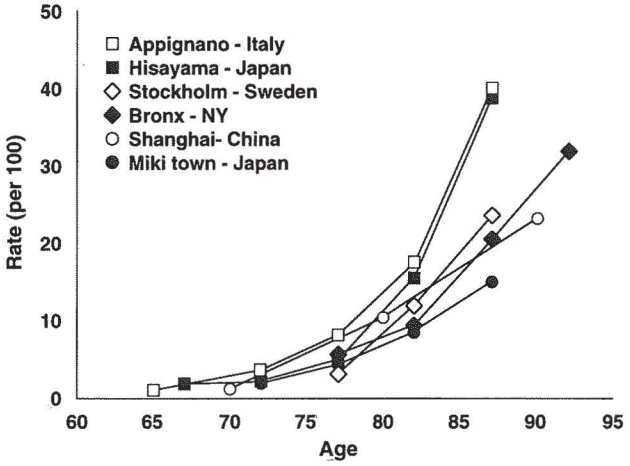

FIG. 1. Prevelance of dementia in studies using DSM-III criteria. Symbols represent data from the following studies: □, Rocca et al. (55); ■, Ueda et al. (58); ◇, Fratiglioni et al. (57); ◆, Aronson et al. (59); ○, Zhang et al. (52); ●, Fukunishi et al. (56).

Age-Specific Prevalence Rates

The most consistent and robust finding in regard to the epidemiology of dementia is the exponential rise in prevalence as a function of age in the 65- to 85-year age range. This age-dependent relationship is independent of the definition of dementia used by investigators. It was first noted in two of the earliest community surveys of dementia, the survey of moderate to severe dementia in Syracuse, New York, based on a random selection of subjects in specific census tracts, carried out by Gruenberg (53) in the late 1950s, and in a total population survey of severe dementia on the island of Samsö, Denmark, carried out by Nielsen (54) at about the same time. This finding of an exponential rise in prevalence with age is also true of the most recent studies (52,55–61). Studies using DSM-III criteria for the diagnosis of dementia are plotted in Fig. 1.

Jorm et al. (38) used data from 22 studies carried out before 1985 to determine the coefficients for this exponential rise. Despite marked differences in overall prevalence, they reported that "the relationship between prevalence and age was found to be consistent across studies, with rates doubling every 5.1 years" (the 95% confidence limits were 4.79–5.37 years). We have found that the semilog plot used by Cross and Gurland (62) is very useful in visualizing this relationship since the exponential curve then becomes a straight line as shown in Fig. 2, which includes age-specific prevalence data from several recent studies using a variety of diagnostic criteria (38,43,46,52,55–59,63). The regression line, based on the Jorm et al. summary of the 22 earlier studies, fits these newest data remarkably well in regard to the age–prevalence relationship.

The problem with this model is that it predicts that everyone would become demented by age 100 or sooner depending on the exponential coefficient. We know this is not true. Many centenarians are cognitively intact and quite vigorous. In the fall of 1980, Richard Meyer, a British businessman-philanthropist who was knighted on his 100th birthday, toured the United States at age 100 years and 6 months to raise money for his philanthropy, Concerts for Children. He lectured to the music faculties at Sarah Lawrence and Princeton, attended a number of fund-raisers, and met with the National Endowment for the Humanities in Washington, D.C.—all within a 10-day period! Some centenarians even remain creative: Mary Robertson ("Grandma") Moses produced 25 of her masterpieces after age 100.

If the exponential or log relationship between age and dementia prevalence holds so well between ages 65 and 85, but not over the age of 85, what model should be used? Dewey (64) has suggested several other models including logit and probit models; we have plotted these various models in Fig. 3. We cannot distinguish between these models on the basis of existing data; community surveys of dementia in centenarians, including nursing home as well as community-dwelling subjects, need to be carried out.

There are, however, considerable data in regard to subjects in the 85-year age range, but these show

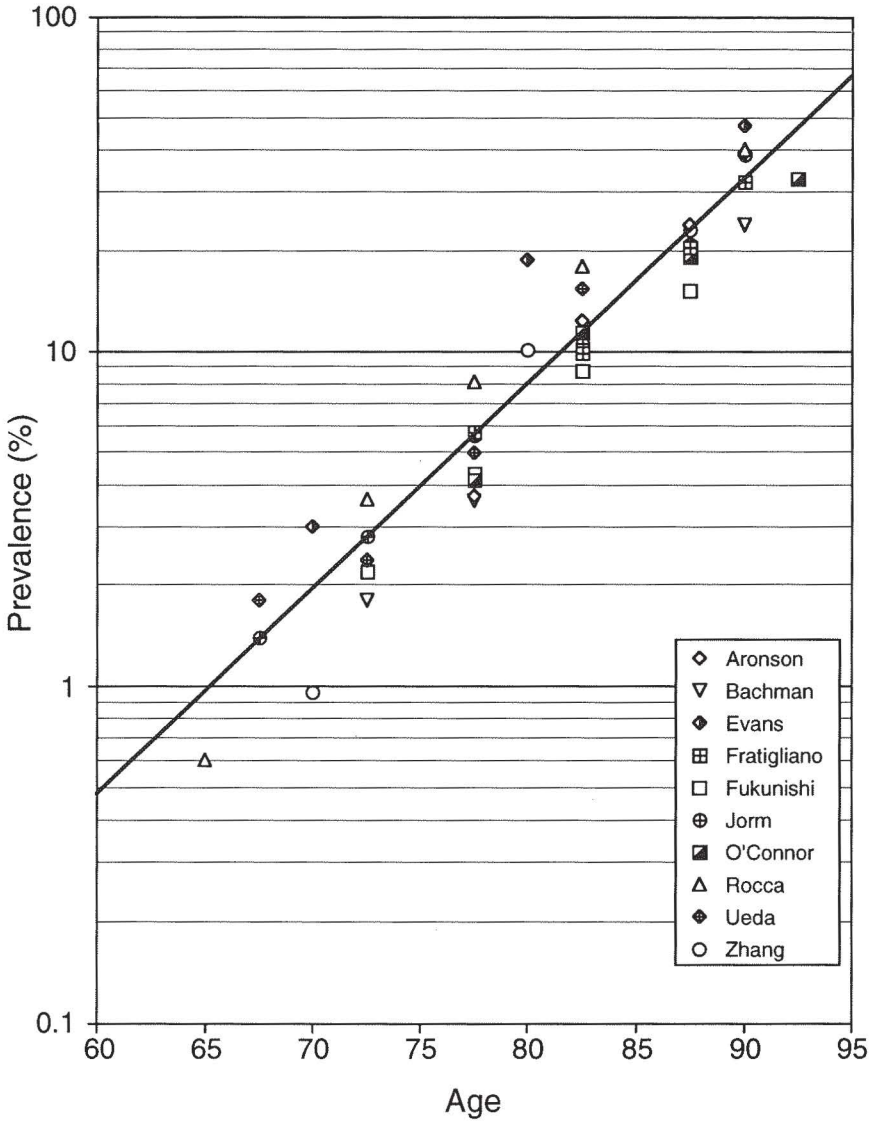

FIG. 2. Semi-log plot of prevalence data comparing the Jorm regression line with a number of recent studies (38,43,46,52,55–59,63).

marked differences in dementia prevalence among studies as is evident in Figs. 1 and 2. As those over age 85 represent the fastest growing segment of the United States population, these differences in prevalence rates would have significant public health impact for projections of social and fiscal costs of dementia (65).

In addition to the methodological problems that we have discussed as a possible explanation for these differences in prevalence rates, additional factors include the relatively small number of individuals in the over-age-85 samples as well as differences in local custom concerning institutionalization of the very elderly. But real cohort differences may exist; certainly differences among countries as to socioeconomic conditions and educational opportunities were greater at the turn of this century than they are today in regard to the countries that have been surveyed.

The first study that specifically focused on 85-year-olds was reported by Skoog et al. (66), who surveyed half of all persons born between July 1, 1901, and June 30, 1902, and registered as living in Gothenburg, Sweden. Of the 783 living subjects selected, 37% refused either initial interview or follow-up examination. Of the remaining 494 subjects who underwent full evaluation, 29.8% met DSM-III-R criteria for mild, moderate, or severe dementia; thus 70.1% were nondemented. This is surely an underestimate of the prevalence of dementia in 85-year-olds considering that 275 declined to participate or come to the final evaluation. But even in the unlikely event that all of the noncompliant had been demented, at least 44% of the 85-year-olds were nondemented. Perhaps this survey sets useful limits on the prevalence of dementia at advanced age in a total community cohort.

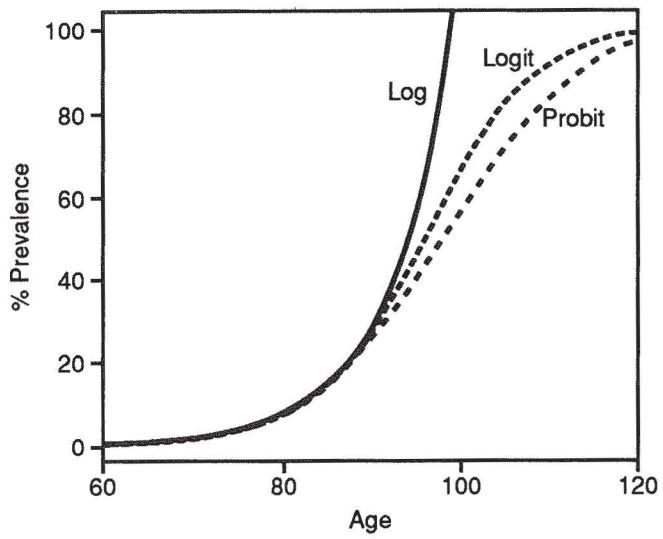

FIG. 3. Comparison of log, logit, and probit plots of prevalence data from the studies that used DSM-III criteria.

Education, Occupation, and the Prevalence of Dementia

In 1988, Mortimer (67) predicted that low education would be a positive risk factor for dementia in the very elderly. Zhang et al. (52) confirmed this prediction in the Shanghai survey of dementia. Over one-quarter of that cohort had never received any formal education, and the prevalence of dementia *after age 75* (but not at earlier ages) was increased markedly in the uneducated. Although diagnoses of dementia were made clinically in these cases, the investigators were concerned that life-long impairment in cognition might have been misinterpreted as dementia. Hill et al. (44) showed, however, that the education effect remained if algorithmic diagnoses based only on history and measures of instrumental activities of daily living, such as that of Pfeffer et al. (45), were made. That education is protective against functional impairment during aging has also been reported by Snowdon et al. (68) in their study of Catholic nuns over the age of 75. Since these initial reports, other studies have confirmed the effect of very low education (69,70).

In regard to occupation, there is now one case–control study in which subjects were matched for education (32) and two prevalence studies (55,71) that report a significantly increased prevalence of dementia in manual laborers. In addition, White et al. (72) have shown that low occupation is an independent risk factor for incident cognitive impairment in a longitudinal study, taking into account age, gender, education level, and history of stroke.

Gender and Risk of Dementia

In contrast to the obvious effect of age and the very likely importance of education and occupation in regard to the prevalence of dementia and AD, the effect of gender is inconsistent. In many studies the prevalence rates for AD are significantly higher in women than in men, whereas the prevalence rates of vascular dementia are sometimes higher in men. Heyman et al. (73) reported an increased prevalence of dementia in black women, but no gender differences among white subjects. In the Shanghai survey (52) a logistic regression that included age, education, and gender showed that female gender was an independent predictor of dementia. It is, however, uncertain how much of this effect is due to differential longevity of demented women. For example, in the Framingham prevalence study (46), the female/male ratio for cohort members 75 years of age and older was 1.8 for all dementia and 2.8 for AD. But in the Framingham incidence study (74), there was no gender difference in incidence of dementia or AD, leading the investigators to attribute their prevalence findings to differential survival after onset of dementia. In Japan, where the frequency of vascular dementia is greater than AD, men were found to be at a greater risk. Thus, in the Ueda et al. (58) survey the ratio of women/men was 1:2, but in the Fukunishi study there was no gender difference. In addition to differences in longevity, there are differences in education between men and women in many of these cohorts, which might confound the gender difference if not included in the analysis.

Other Demographic Factors and the Prevalence of Dementia

Many basic issues regarding the prevalence of dementia and AD are still indeterminate. These include potential racial differences and urban/rural differences. Although a preliminary study in Nigeria suggested a relative absence of dementia in black populations (75), studies in the United States report higher rates for black subjects than for white subjects (41,73). Although some 1960s studies of purely rural communities had significantly lower rates than other studies [e.g., Akesson (76)], these rate differences might be due to differences in methodology or to the employment of total population assessment. The latter could explain the results since even in urban studies, total population surveys tend to have lower rates than studies that examine only a random sample (38). The prevalence of dementia was not lower, however, in the total community sample in the village of Appignano in Macerata Province, Italy, a very rural area (55). A bet-

ter understanding of these issues will undoubtedly emerge from studies currently in progress.

The Relative Prevalence of AD and Vascular Dementia

In the clinical setting, the diagnosis of probable AD based on the NINCDS/ADRDA criteria is a highly accurate one. In the community, however, there is a greater likelihood of coincident factors that increase the difficulty of diagnosing AD. Two of the major factors are alcoholism and cerebrovascular disease. Because in many populations elderly males are particularly prone to strokes, the differentiation of a concurrent stroke in AD patients and vascular dementia is often unsatisfactory. Two frequently used tools for the diagnosis of vascular dementia, the Hachinski ischemic index (49) and the Rosen (50) modification of the Hachinski index have been shown by Rosen et al. not to differentiate vascular dementia from mixed AD and vascular dementia (50,51). Surprisingly large differences have been observed among community studies in regard to the proportion of subjects diagnosed as having AD or vascular dementia (77). Studies from Japan (56,58,78) show a preponderance of subjects diagnosed as vascular dementia. In contrast, 84% of the subjects in the East Boston study (43) were felt to be suffering from AD. In a study of randomly selected 85-year-olds in Gothenburg, Sweden, Skoog et al. (66) based their differential diagnoses of dementia on both patients and informant interviews using DSM-III-R and NINCDS/ADRDA criteria for dementia and AD, respectively, and the Erkinjuntti criteria for vascular dementia, the latter incorporating information from CT scanning and neurological history for the diagnosis of vascular dementia (51). The diagnosis of vascular dementia, made in 46.9% of the cohort, was more common than the diagnosis of AD (43.5%); the 8.2% of cases with a diagnosis of "mixed" dementia was included among the vascular cases. There were no significant sex-related differences in prevalence or severity.

THE INCIDENCE OF DEMENTIA

Although numerous prevalence studies of dementia and AD have been conducted, estimates of the incidence (new cases in a specified period) of dementia and AD are very limited (59,74,79–82). Since it is possible that life expectancy for demented individuals differs among societies, one might hope that incidence studies would narrow the variability found among prevalence studies. Moreover, virtually all risk factor studies have been conducted using the case–control paradigm, whereas ideally incident cases should be utilized to determine risk because the former may identify conditions associated with disease longevity rather than the actual risk of developing disease. Most important, when exposure history is obtained prior to the development of disease, it is unlikely to be subject to the bias of selective recall. Methodological problems afflict incidence as well as prevalence studies. The ability to compare incidence rates at different study sites is dependent on similar design, screening, and diagnostic procedures. However, during the past several years, a number of community-based incidence studies with similar designs have been initiated, and within a few years the data should become available.

The same methodological problems involving sampling and case ascertainment that occur in prevalence studies also pertain to longitudinal studies. Two additional possible confounds may occur. In most longitudinal studies there are a significant number of dropouts between evaluations (an exception being the Lundby study, which maintained a 98% participation rate); since individuals developing symptoms of dementia may preferentially choose to discontinue participation, the incidence of dementia might be underestimated. Another possible confound is the differential mortality of dementia patients. This is especially important in regard to studies with long intervals between evaluations such as the Lundby and Shanghai studies. In the Lundby study, in which evaluations were carried out at 10- and 15-year intervals, the investigators interviewed families of those who had died in the interim in regard to the status of the subjects, but the validity of this procedure is uncertain. In the Shanghai survey of dementia in which part of the cohort was reevaluated after 5 years, the investigators will use analytical approaches to estimate cases of dementia that may have developed in those who died between evaluations.

From the few available studies the incidence of dementia rises sharply with age over the span of ages between 60 and 85 years. In the Bronx Aging Study, the annual incidence of dementia reached 6% in those over age 85 (59), but in the Lundby study there appeared to be an actual drop-off in rate after age 90 to below 2% (79). Differences in incidence rate between these studies are to be expected because they used very different designs, evaluations, and criteria, but the difference in age trends is unsettling. An annual incidence of dementia of 1% per year in those 70 to 79 years old was reported in the Lundby study (82), but a similar incidence rate was observed in the Bronx (59) and Framingham (74) studies at ages 75 to 80 and at ages 75 to 84 in the Liverpool study (81); an incidence of 3% per year was observed in those 80 to 84 in the Bronx study and in those over 85 in Liverpool. These

discrepancies are quite significant and their resolution must await data from current ongoing longitudinal studies.

Longitudinal Studies of Dementia

Because of the importance of the data derived from these studies, several of the major studies, completed or ongoing, are described.

The Lundby study was the first longitudinal analysis of dementia. In this study of a total population from a geographic area in Sweden, 2,612 persons were prospectively followed by Hagnell and associates (79,82–86) over a 25-year period. Examinations were conducted in 1947, 1957, and 1972. Evaluations were based on informant interviews, subject interviews, and observations of subjects; however, formal mental status and neuropsychological and neurological examinations were not carried out. Initially, the subjects were described in terms of "age psychosis" and "arteriosclerotic psychosis," but have been reclassified by Rorsman et al. (82–84) in terms of AD and vascular dementia. Incidence rates per year of developing AD or MID were calculated. The lifetime risk of developing AD was calculated at 25.5% for men and 31.9% for women, although rates for men were slightly higher than for women until age 80. Multi-infarct dementia was more common in men (29.8%) than in women (25.5%). Additional analyses of family history and other risk factors are in progress.

The Baltimore Longitudinal Study of Aging (BLSA) is a prospective study of normal aging that has been conducted since 1958. Initially limited to men, enrollment of woman began in 1978. The effort has included more than 1,900 subjects and is now part of the Gerontology Research Center of the National Institute on Aging.

An initial study of dementia in this cohort was conducted by Sluss et al. (80), who performed chart review of active BLSA male participants and estimated the incidence of AD to be 3.2 per 100 person years at age 80. Since there may be a tendency for men with AD to withdraw or fail to return for examination, the inclusion of only those subjects who were active in the study could result in underestimation of the probability of developing AD. In addition, diagnosis of dementia was determined by review of information available from BLSA research charts rather than examinations with appropriate laboratory studies. Follow-up of the BLSA subjects diagnosed with dementia was reported by Arenberg (87), who found that 22 of the 27 cases were performing well on cognitive tests concurrently or several years after the presumptive diagnosis, suggesting possible misclassification.

A new effort using NINCDS/ADRDA criteria for AD is currently under way in the BLSA. A survey of deceased participants is being included along with examination of active and inactive subjects. This approach will allow the examination of risk factors such as head trauma without case recall bias.

The Framingham study (46,74) began with a general population sample in the town of Framingham, Massachusetts, in 1950. There were 5,209 men and women aged 30 to 62 initially enrolled and followed every 2 years with the primary focus on risk factors for cardiovascular diseases. In 1976 and 1978 a brief screening examination was carried out by a neuropsychologist at which time the cohort included 2,828 subjects. Beginning in 1982 the Mini–Mental State Examination (MMSE) was administered at each biannual examination and detailed evaluations were carried out on those below education-computed MMSE cutoff scores. Patients diagnosed as demented were classified as mild, moderate, or severe, but prevalence and incidence figures were limited to those with moderate or severe dementia based on functional criteria.

The Bronx Aging Study (59,88,89) began in 1980; 488 nondemented subjects, ages 75 to 84 years, were recruited. The study was unique at the time in that each subject received both an intensive medical and an intensive dementia workup, the latter including neurological and neuropsychological evaluations on an annual basis. Multiple laboratory tests both for cardiovascular disease and dementia, the latter including brain imaging, were carried out as indicated. Diagnoses of dementia were based on DSM-III and NINCDS/ADRDA criteria. However, this was a volunteer rather than a population sample and is subject to self-selection bias. In particular it is likely that a few subjects joined the study because of their perception of early memory problems, and, although the subjects selected tested within normal limits at entry, this may have enriched the sample with subjects at risk for dementia. As we have already noted, an opposite bias may exist in population samples in which there is often a high dropout rate that may be enriched with subjects undergoing cognitive changes who no longer wish to participate in neuropsychological testing.

The Shanghai Survey of Dementia began in 1987 when 5,055 randomly selected residents, age 55 and over, living in the Jing-An district of Shanghai were sampled by neighborhoods, based on a randomized cluster sampling technique developed by Levy et al. (90). Oversampling of the elderly was accomplished by screening individuals age 55 and over in one-third of the randomly selected neighborhoods, individuals 65 and over in one-third, and individuals 75 and over in one-third. During the screening interview, demographic data and a medical history were obtained from the subject or from an informant, and a Chinese version of the Mini–Mental State Examination (CMMS) was given to the subject (90,91). The 510 subjects who

scored below education-adjusted CMMS cutoff scores together with a stratified 5% sample of those who scored above these cutoff scores underwent an intensive clinical evaluation that included a medical history and physical examination, a neurological examination, a psychiatric interview, and a variety of standard psychiatric, neuropsychological, and functional scales that had been adapted to the Shanghai cohort. Dementia was diagnosed on the basis of the DSM-III criteria (1) and AD on the basis of the NINCDS/ADRDA criteria (2). A second screening and evaluations of subjects age 75 and over was carried out in 1988, and the entire living cohort was reevaluated in 1992. The 1992 survey is now being analyzed and will provide incidence and risk factor data on this cohort. The sample differs dramatically from Western samples in terms of life-long socioeconomic conditions—for example, 27% of the sample had received no formal education whatsoever—but it represents a true community sample with a very high compliance rate.

Liverpool: In the mid-1980s Copeland et al. (81) studied a cohort of 1070 community-living persons aged 65 and over using the Geriatric Mental State (GMS) interview that they had developed, together with a computerized algorithm (AGECAT) for making diagnoses. Three- and six-year follow-ups were obtained, and the incidence of dementia was calculated based on the 3-year follow-up with diagnoses confirmed at year 6. They report an incidence for all dementias of 0.38 per 100 person years at ages 65 to 74, 1.18 per 100-person years at ages 75 to 84, and 2.87 per 100-person years in those age 85 and over.

EURODEM: From numerous studies being conducted in Europe, six studies have been designated as EURODEM incidence studies: PAQUID (Bordeaux, France), Italian Longitudinal Study of Aging, Rotterdam Elderly Study (Netherlands), Zaragoza Study (Spain), Multicenter Study of Cognitive Functioning and Aging (United Kingdom), and Alpha Study (Liverpool, UK). To minimize methodological differences, a core protocol was adopted. It includes (a) two assessments of the population, at least 2 to 3 years apart; (b) sample size >4,000; (c) inclusion of community and institution dwellers; and (d) a two-phase case-finding procedure with common screening and diagnostic methods. Collaborations of this type will allow effective comparison of the rates and risk factors derived from these different studies over the next decade.

MORTALITY

The evidence that dementia shortens life expectancy goes back to the classic 1955 study of Roth (92), who demonstrated that survival was markedly shortened in elderly mental hospital inpatients with "senile psychoses" and "arteriosclerotic psychoses" as compared with inpatients with depression or schizophrenic disorders (paraphrenia) of the elderly. Wang and Whanger (93) in the early 1970s summarized a number of clinical studies of subjects with AD and Pick disease; subjects with presenile dementia of the AD and Pick type lived on the average 6.8 years as compared with expected survival of 21.5 years; those with onset in the senium, 5.1 years versus the expected 9.6 years; and those with arteriosclerotic brain disease, 3.8 years versus the expected 14.0 years. In a later clinical series, Barclay et al. (94) reported longer life expectancies from onset of 8.1 years for dementia of the Alzheimer type and 6.7 for MID, but again with a major reduction in expected survival. Similar findings have been reported in other recent series (95). In a cohort of 323 patients who had been referred to an outpatient department because of suspected dementia in the early 1980s, 49% of the AD patients and 63% of those with vascular dementia had died in 1989 compared with 1.7% of those with functional memory problems (96). In this study, mean survival using life table analysis with the product limit method showed that survival from symptom appearance was 10.3 years in AD and 8.0 years in MID. The authors suggested that life expectancy of dementia patients has increased over time but remains significantly different from that of nondemented individuals.

Available community studies confirm the malignancy of dementia. Nielsen et al. (54,97) identified all cases of severe dementia on the island of Samsö, Denmark; 5 years later none of these subjects was alive, in contrast to individuals with depression or without cognitive impairment who had a much better survival. Evans et al. (98) studied mortality in the follow-up study of East Boston subjects, using the Cox proportional hazard model to adjust for age and gender. There was a significant increase in risk of death conferred by AD, but the odds ratio was only 1.4. This risk increased in patients showing debility from AD. A much greater effect of AD and vascular dementia on 5-year survival was observed in the Shanghai study (99).

These investigators used a multivariate analysis, the Cox proportional hazard model, to determine the relative risk of dying based on 5-year vital data obtained on the 3,153 subjects age 65 and older who participated in the 1987 population survey of dementia in Shanghai, China, taking into account not only age, gender, and education level but also 15 prevalent medical conditions reported in the initial 1987 survey. The mortality risk ratio was 5.4 (95% CI = 1.4–14) for AD and 7.2 (95% CI = 3.6–14) for "other dementias" (a category that included predominantly vascular dementia), similar to the mortality risk ratio of cancer (RR = 5.5; CI = 2.9–11) in those aged 65 to 74. In those aged

75 years and older the mortality risk ratios were 2.7 (95% CI = 2.1–3.6) for AD and 3.5 (95% CI = 2.5–4.8) for "other dementias." In those aged 75 and older the population attributable risk of death due to the dementing disorders was 20.5%. Thus, both AD and vascular dementias were truly malignant. Certainly, in this population these dementing disorders constituted a major risk factor for death in the elderly over age 75. If similar figures held in Western countries in which life expectancy is about 76 years, then 10% of *all* deaths would be attributable to the dementing disorders.

RISK FACTORS FOR AD AND CAUSALITY

Do the putative risk factors for dementia and AD that we have discussed meet accepted epidemiological criteria for causality (100)? These criteria include strength of association between risk factor and outcome, consistency between studies, a dose–response relationship, appropriate temporal relationship, and biological plausibility. This section considers which of the risk factors we have discussed meet these criteria and can be causal, and to what extent these putative factors account for existing cases of AD.

Family history has been consistently demonstrated to be a risk factor for AD. Many excellent studies in this regard have concentrated on the question of whether the familial association is genetic. This is no longer at issue since specific point mutations on the amyloid precursor protein (APP) gene of chromosome 21 have been identified in a small subset of early-onset AD (101–103). Within the past year linkage studies have identified additional gene loci on chromosome 14 (104–107), accounting for the majority of early-onset kindred. There is also evidence for linkage to a chromosome 19 site in late-onset cases (108). See also the chapters by Bird and St. George–Hyslop.

It has been argued by some geneticists that a large proportion of AD patients are due to a gene (now, gene*s*) with an incomplete but age-dependent penetrance (109,110). However, the relative difficulty recently encountered in finding large numbers of families with strong autosomal dominant pedigrees and the discordance observed in many identical twin pairs (111–113) are inconsistent with this concept. On the other hand, a positive family history of AD (that is, a history of AD in a single first-degree relative) meets the epidemiological criteria of causality: a strong association (relative risk between three- and fourfold), consistency among studies, appropriate temporal relationship, a relationship between the degree of exposure and the disease (a "dose–response"), and biological plausibility (the APP mutations).

Increasing evidence is accumulating that head injury meets the epidemiological criteria of a causative factor for AD. In a recent and meticulous case–control study, Graves and associates (16) found that head trauma leading either to concussion or a visit to a doctor was strongly associated (relative risk greater than threefold!) with subsequent development of AD. Graves et al. note in their review that there has been striking consistency in regard to the strength of association between head injury and AD among case–control studies, whereas much lower ratios were found in one retrospective and in one prospective longitudinal study. The EURODEM reanalysis (17) confirmed the strength and consistency of this association. The key issue is whether recall bias can account for the increase in history of head trauma in the case–control studies, where the concerned informant or family may often have reflected on past events and selectively recalled more events of head trauma, as compared with the number of events of head trauma recalled by controls or by the informants or families of the controls.

Katzman (69) has recently reviewed the available data in regard to the protective effect of education shown in Table 2. It is evident from the data in this table that there is a consistent and significant effect, with a risk ratio of about 2, when noneducated are compared to those with more than 6 years of schooling. In the Shanghai survey a risk ratio of 4.9 was found for the development of clinically diagnosed AD when noneducated are compared to those with more than 6 years of schooling. A lesser effect, that does not reach significance, is present when those with elementary education are compared to those with secondary schooling.

BIOLOGICAL PLAUSIBILITY

In regard to biological plausibility, there have been many advances in our understanding of the cellular and molecular basis of AD. There is a good agreement that the final cellular event that leads to cognitive impairment is loss of neocortical and hippocampal synapses (115–118). One plausible hypothesis in regard to low education as a risk factor is that noneducated individuals have a reduced brain reserve (51,67) probably due to a lesser synaptic reserve (69).

But in regard to which of the many molecular and cellular changes that occur prior to synapse loss are the critical ones, there is now strenuous debate as indicated in this book in the chapters by Terry et al., Davies, Cotman and Pike, and Robakis. The essence of this debate centers around the etiological role of amyloid. At the current stage of knowledge, one can argue that the epidemiological data is most easily interpretable if *diffuse* β-amyloid containing plaques do play a central role. In individuals with Down syndrome, a condition in which AD pathological changes

TABLE 2. *Effect of no or low education on prevalence of dementia and AD*

	Survey population		Diagnostic criteria	Number demented	Illiterate vs secondary+	Primary vs secondary+
	N	Age				
Shanghai (52)	5,055	55+	DSM-III for dementia	159	2.98† (<.0001)	1.29† n.s.
			NINCDS/ADRDA for AD	107	4.80† (<0.0001)	1.71† n.s.
Bordeaux (60)	2,792	65+	DSM-III for dementia	101	1.94†† (<0.0008)	1.09†† (0.02)
Stockholm (57)	1,810		DSM-III-R for dementia	216		1.94*(<0.001)
			DSM-III-R for AD	109		1.47* n.s.
Appignano (55)	779	60+	DSM-III for dementia	48	7.2% of illiterate, 0.5% of >5 yr	2.8% of 5 yr+, 0.5% of >5 yr
Finland (40)	8,000	30+	Modified DSM-III to exclude mild dementia	163	Illiterate > secondary	Primary < secondary
Ashkelon (70)	1,399	75+			Illiterate > secondary	Primary > secondary
Cambridge, England (114)	2,302	75+	DSM-III using CAMDEX	242		1.31 n.s.**

Modified from Katzman (69).
†Odds ratio in entire cohort of 5,055 determined by logistic regression; terms included diagnosis, age, education, and gender.
††Relative risk determined by use of Cox model, including age (60).
*Odds ratios calculated from data in reports, using the Mantel-Haenzel statistic.
**Demented subjects who left school prior to age 15 compared to subjects with longer education.

occur uniformly in the brain by age 40 and in which the pathology is attributed to the additional genes resulting from the triplication of chromosome 21, including the APP gene, *diffuse* β-amyloid–containing plaques in neocortex (defined as focal collections of β-amyloid without neuritic involvement) are present in the brain as early as age 10 (119), 20 to 30 years before the development of the full panoply of AD changes observed in the Down brain. The known familial AD (FAD) mutations at codons 670/671 and 717 on the APP gene flank the β-amyloid sequence and are consistent with this mechanism. The core of the neuritic plaque contains, in addition to β-amyloid, other proteins, sometimes termed chaperone proteins, that are thought to participate in the conversion of soluble β-peptide to β-amyloid; these include α-$_1$-antichymotrypsin, complement, and apolipoprotein E (ApoE) (120). Promoters for APP include c-*fos* and heat shock proteins. Genes for α-$_1$-antichymotrypsin, c-*fos*, and one of the heat shock proteins are located on chromosome 14 near the chromosome 14q24.3 marker for the early-onset familial cases. The gene for ApoE is located on chromosome 19 near the marker for the late-onset FAD marker.

Recently, ApoE alleles were studied in autopsy-confirmed AD patients from 30 families with multiple affected members (28 had late onset, after age 60) and in nondemented controls. There was a higher frequency of ApoE4 in AD (52%) than in nondemented controls (16%), $p = .01$ (121). ApoE4 also bound soluble β-amyloid peptide more avidly than did ApoE3; antibodies to ApoE stain amyloid deposits in AD and other amyloidoses (120,121). Roses et al. (122) have found that the ApoE4 allele is present in over 65% of the cases with late-onset FAD and 50% of the cases of sporadic AD with onset between ages 65 and 80, whereas it is present in only 30% of controls. This may represent a major finding, although it needs to be replicated. These investigators reported that the ApoE4/E4 allele that is normally present in 3% of the population increases the odds of getting AD sevenfold; the ApoE4/E3 allele, which is present in 23% of the population, increased odds 3 to 4 times. If so, one might speculate that over 30% of the cases of AD with onset between ages 65 and 80 could be attributed to the ApoE4 allele. If the effect of ApoE4 is due to its avid complexing with the soluble β-amyloid peptide, then it is possible that the three genes involved in familial AD all act through a single mechanism involving β-amyloid, but there is no direct evidence for mutations in any of the candidate genes on chromosome 14.

In addition to a possible relationship between genetic factors and amyloid, diffuse β-amyloid plaques occur in relationship to two of the other putative risk factors that we have described, head trauma and myocardial infarct. Head trauma might act by production

of diffuse plaques as occurs in Down syndrome. The promoter region for the β-amyloid precursor protein (APP) gene contains "heat shock" promoter elements that could be activated by such insults as trauma, anoxia, and alcohol as well as a c-*fos* promoter element that could be activated by these and other stress events leading to the production of excessive amounts of APP and an increase in its degradation to β-amyloid with the development of β-amyloid–containing diffuse plaques. In some cases the brains of boxers with dementia pugilistica have been found to contain neocortical diffuse plaques in the typical Alzheimer pattern (123) in addition to the neurofibrillary tangles that are present in a subcortical distribution in these brains. Recently it has been reported that one-third of young adult subjects dying within 3 years of a serious head injury have diffuse plaques in their brain.

In their longitudinal study of 75- to 85-year-old nondemented volunteers, Aronson et al. (89) found that myocardial infarct was a risk factor for dementia, in elderly women in particular. Although this has been found to be a risk factor in only one study, the report is of interest because Sparks et al. (124) have found that in autopsies of older individuals who died without dementia but who had over 75% constriction of a coronary vessel, there is a marked increase in the number of diffuse plaques in the brain as compared to age-matched individuals who did not have severe coronary disease.

EPIDEMIOLOGY OF AD: A PUBLIC HEALTH PERSPECTIVE

The epidemiological evidence that AD will become increasingly the dominant disorder in late life—both in terms of its increasing prevalence as the population ages (65), and the recent advances in identifying risk factors in AD—may have widespread social impact. If the sum of the evidence in regard to risk factors presented above is correct, we may already know as much about the major risk factors for AD as is known about risk factors for other major chronic diseases, such as myocardial infarct and cancer. But in regard to our understanding of these putative risk factors, there are also major reservations. The question of what proportion of cases are associated with family history can more directly be addressed by the epidemiological evidence. The risk of developing AD is increased three- to fourfold if one has a first-degree relative with the disorder. From a population perspective, it becomes possible to calculate the "attributable" risk, knowing the frequency of the risk factor in the matched, nonaffected population and the relative risk or odds ratio. Mortimer (125) calculated the attributable risk due to family history as 26%; that is, in the groups studied 26% of all AD cases could be attributed to probable genetic factors. In regard to head injury (with concussion), using the relative risk reported in the EURODEM reanalysis (18), the attributable risk due to head injury is about 5% to 7% of cases of AD. This risk is most straightforward in those with onset of AD before age 75.

In the elderly, those in whom AD begins after the age of 75, the data on the risk factors are not as certain as in those with onset at earlier ages. In particular, the role of family history in this cohort is difficult to evaluate, in part because mothers and fathers often died at an early age. Also, the number of case–control studies in this age group has been limited. From the sparse data available, head trauma appears to play a significant although lesser role, perhaps because the number of cases per year due to head trauma remains fairly static while the total number of cases rises exponentially with age, relegating this risk factor to a lesser role. In this older age group however, lack of or low education becomes a highly significant risk factor, now meeting all of the Bradford-Hill criteria. And in the very elderly, with onsets for the most part after age 80, there is evidence from a single study that myocardial infarct may be a risk factor (89). In the Bronx Aging Study, myocardial infarct increased the risk of AD threefold among elderly women and accounted for 20% of the cases of AD in this group. There was also an increase in risk among elderly males but this did not reach significance possibly due to the sample size. If this risk factor could be extrapolated to the general population, it would account for another 10% to 15% of the attributable risk, but the finding needs to be confirmed by other studies of the very elderly.

If these risk factors are simply additive at the population level, family history and head trauma together would account for 31% of the attributable risk for AD and when an additional 10% to 15% is added due to the attributable risk from coronary heart disease in elderly women, 41% to 46% of the attributable risk for AD may be known. And this does not take into account the cases due to low education. By way of comparison, the attributable risk of heart attacks from obesity, high cholesterol, lack of exercise, and diabetes together is about 40%!

AD AS A CHRONIC DISEASE

The foregoing epidemiological and biological advances suggest a view of AD as a chronic disease in the sense that the term is used by epidemiologists to describe atherosclerotic heart disease and cancer. The picture emerging is that of a long preclinical period, a period in which intervention to prevent the development of dementia may be possible. Perhaps decades

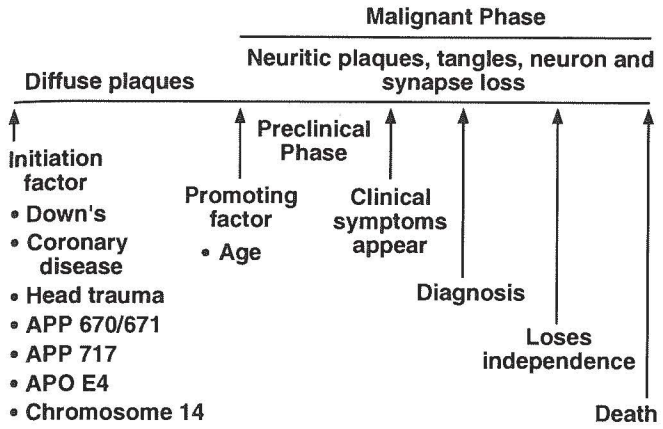

FIG. 4. AD as a chronic disease: cancer model.

before the onset of clinical symptoms, as initiating factor, the diffuse plaque, is laid down as the result of genetic, traumatic, anoxic, and perhaps other events (Fig. 4). At some point the intracellular events leading to neuritic degeneration, neurofibrillary tangles, and synapse loss begin, perhaps due to the action of the β-amyloid itself, but very likely requiring a different and not yet understood promoting factor(s). At this point the AD changes may be conceived to have entered a malignant phase and continue to progress on their own, leading to the irreversible decline that is the tragedy of AD. Clinical symptoms begin to appear when the number of synapses falls below a threshold level or when acute stressors exceed the brain's capacity to respond effectively. It is at this stage of the pathogenetic process that it is likely that lack of education and perhaps later life cognitive inactivity play a role by decreasing synaptic reserve. This concept is illustrated in Fig. 4.

There are still many uncertainties in regard to the evidence at hand. The assumed central role of amyloid is in dispute. Putative factors need to be confirmed prospectively. If it turned out that the head trauma effect were largely or entirely due to recall bias, much of the preceding argument would be meaningless. Similarly, the effect of myocardial infarct is based on only one epidemiological and one pathological study. It is critical that these weaknesses be addressed, particularly in the context of longitudinal studies carried out on community samples or well-defined cohorts in which the history of exposure to putative risk factors is obtained in detail before the development of dementia. If this overall picture proves to be correct there are important societal implications.

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