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Development of Dementing Illnesses in an 80-year-old Volunteer Cohort

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We have prospectively followed over a 5-year period 434 volunteers who were at intake ambulatory, functional, presumably nondemented, and between 75 and 85 years of age. Fifty-six (an incidence of 3.53 per 100 person-years at risk) developed a progressive dementia: 32 met diagnostic criteria for Alzheimer's disease (AD) (an incidence of 2.0 per 100 person-years at risk), 15 had vascular or mixed dementia, and 9 had other disorders or remain undiagnosed. New cases of dementia were as common as myocardial infarction and twice as common as stroke. Risk factors for both dementia and AD were age (over 80) and gender (female); other reported risk factors such as family history, prior head injury, thyroid disease, maternal age, and smoking were not risk factors for AD in this elderly cohort. Prior stroke was the major risk factor for vascular or mixed dementia; diabetes and left ventricular hypertrophy but not a history of hypertension per se were also risk factors for vascular dementia. The major predictor of the development of AD was the mental status score on entry. The 58.5% of the cohort who made zero to two errors on a 33-item mental status test had a less than 0.6% per year chance of developing AD, whereas the 16% of the cohort with five to eight errors on this test developed AD at a rate of over 12% per year. Thus, it is possible to identify a large cohort of 80-year-olds who are at low risk for AD and a smaller cohort at very high risk.

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It is well recognized that the assumption that "senility" (that is, senile dementia in current terminology) is an inevitable consequence of aging is not true. As the number of elderly persons has increased, it has become apparent that many octogenarians, nonagenarians, and even centenarians remain mentally alert. Nevertheless, the prevalence of dementia is known to rise quite sharply with age. Thus, the prevalence of severe dementia at age 65 is less than 1%, and at age 85, 15 to 20% [9, 16, 23]. Because we were interested in observing the onset of dementia, we chose to study a group of subjects whose ages made it likely that a significant proportion would develop one or another of the disorders that produces dementia.

The term *dementia* is currently understood [2] to refer to a symptom complex that may be caused by a variety of neurological and systemic disorders [10], but most commonly by Alzheimer's disease (AD), which usually accounts for 50 to 60% of the cases, and by multiinfarct dementia (MID), which usually accounts for 10 to 25% of the cases [15, 29, 30].

We report here a prospective, longitudinal study of the development of dementing illnesses in a group of ambulatory, active, presumably nondemented volunteers aged 75 to 85 years at intake. Our objectives in carrying out this study were to determine the incidence of AD, MID, and other dementing disorders in this volunteer cohort, to identify risk factors specific for AD or MID, and to identify measures most helpful in the early diagnosis of dementia in an elderly population. As it is difficult to define the boundaries of cognitive and functional impairment precisely, in part a consequence of the insidious onset of the most common of the dementing disorders, AD, our strategy has been to use repeated evaluations of subjects who have shown changes in cognitive and functional measures until a firm clinical diagnosis could be made.

Methods

We enrolled and evaluated 488 volunteer subjects and obtained at least one repeat evaluation on 434. At intake, the subjects were 75 to 85 years old except for a few individuals just under 75 or over 85 who were leaders of community organizations that helped with the recruitment effort. The

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subjects were ambulatory, functional in their community, and presumably nondemented. Exclusionary criteria were the presence of Parkinson's disease, terminal illnesses, or visual or hearing impairments that precluded psychological testing. Subjects agreed to participate in annual reexaminations. During the first 3 years of follow-up, 12% of the sample was lost to follow-up, and 9.8% died. The initial information-memory-concentration (IMC) test [5] error score of the subjects lost to follow-up (2.78 ± 2.4 [SD]) and the initial IMC error score of subjects who died (2.65 ± 2.2) did not differ significantly from the initial IMC error score of the cohort who returned for follow-up.

Subjects were recruited from senior citizen centers, by local newspaper advertisements, and by word of mouth. Potential volunteers were told that they would be offered a comprehensive yearly evaluation. All subjects gave informed consent and understood the longitudinal nature of the study. There was no direct payment for participation, but transportation costs, lunch, and certificates of participation were provided for each subject. Because some subjects delayed their reexaminations, the average time to reexamination was 15 months. Intake occurred over a 3-year period; our subjects have been followed from 2 to 5 years for an average of 45 months.

The initial evaluation required 2 days to complete; subsequent annual evaluations required 1.5 days each. The initial evaluation included the following: psychosocial interview; educational, occupational, residential, and social history; risk factor interview; family history, including current age or age at death and the presence of memory symptoms or dementia in each first-degree relative, as well as the presence of Down's syndrome; medical history; current and past medication; and life stress interview. All evaluations included a mental status examination, functional rating, neuropsychological evaluation, the Zung and Feighner depression ratings, physical and neurological examinations, and the following laboratory tests: hemogram and biochemical screen, electrocardiogram, 24-hour ambulatory Holter monitoring, and plasma lipids and lipoprotein levels [6].

Operationally, we required that subjects make eight or fewer errors on a modification of the IMC test [5] to be accepted into the study; the IMC test has been validated against other mental status tests [28] and against quantitative microscopic features in prospective clinical-pathological studies [17]. This mental status test consists of 26 items, the most difficult being reciting the months backward and a task involving a five-part memory phrase. As several items are weighted, a total of 33 errors can be made. The cutoff score of eight errors for entry into the study was based upon pilot observations at a senior citizens center and previous clinical-pathological series [8, 18].

If on annual reevaluation a change in cognition or function was noted by history or neuropsychological or neurological evaluation, or if there was an increase of four errors or more on the IMC or if the total number of errors exceeded eight, a dementia workup was carried out. The additional workup included an electroencephalogram, a high-resolution computed tomography (CT) scan, Hachinski [11] and Rosen [24] ischemic scores, and a further evaluation by the neurologist with the objective of determining if the criteria for dementia according to the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III) [2] were present. The CT findings were used in the determination of the diagnosis to help identify structural disorders that cause significant dementia: in this series, 1 patient had a glioblastoma and 1 had hydrocephalus. Diagnoses were made by the study neurologist in collaboration with the research team and reviewed independently by a panel of two neurologists and a psychiatrist. If the diagnosis was uncertain on the first clinical examination or if there were differences between evaluators, the subject was reexamined every 6 months until a specific diagnosis could be determined.

The criteria for the diagnosis of dementia were those stated in DSM-III [2]. The criteria for the diagnosis of probable or possible AD were those stated by McKhann and colleagues [21]. We based the diagnosis of MID upon clinical features (including abrupt onset, stepwise deterioration, fluctuating course, evidence of stroke, and focal defects) and the Rosen and colleagues [23] modification of the Hachinski [11] ischemic score; 11 of the 16 subjects with the diagnosis of vascular dementia had infarcts on their CT scan. Neither DSM-III criteria nor the ischemic scoring systems differentiate subjects with pure vascular lesions from those with mixed (MIX) Alzheimer's and cerebrovascular disease [24]. Hence, we designated demented subjects meeting the above criteria as MIX/MID.

In this article we describe the study population, estimate dementia rates, and present results of associations of dementia with several dementia predictors. Statistical analyses included chi-square tests of crude associations. To control for confounding factors, we used stratified analysis [19] and proportional hazards modeling [6].

Results

Description of Population Recruited

This volunteer cohort resided primarily in the northern and eastern tier of the Bronx. The majority (70%) were Jewish, and there were also many subjects of Italian, Irish, and German ethnic backgrounds. The cohort was predominantly (90%) white; 35.5% of the subjects were men and 64.5% were women. The average age at intake was 79 years. Although our subjects represent a volunteer cohort rather than a probability sample, their characteristics were representative of the area from which the cohort was drawn in that, according to 1980 census data, women represent 64.8% of the 75- to 84-year-old age group in the catchment area (total population 731,429) from which the sample was drawn. The area is predominantly Jewish and white, but the white population represents only 61.8% of the area population, indicating that nonwhite groups were not successfully recruited. The modal education was seventh to ninth grade, and the modal socioeconomic status was lower middle class, a majority having worked in a factory at some time during their life. The majority (55.1%) were widowed, 34.2% were married and living with their spouse, 6.1% were separated or divorced, and 5.1% were never married. Although 84.4% were apartment renters, the mean time at their

Table 1. Cumulative Incidence of Alzheimer's Disease (AD) and Dementia (as of December 31, 1985) as a Function of Initial Mental Status Score

Initial Error Score[a]	N	Percent of Sample	Follow-up (person-months)	New Cases of All Dementias	Rate of All Dementias per 100 Person-Years	New Cases of AD	Rate of AD per 100 Person-Years
0	87	20.0	3,826	2	0.63	1	0.31
1	81	18.7	3,877	4	1.24	2	0.62
2	86	19.8	4,065	7	2.07	2	0.59
3	52	12.0	2,234	8	4.30	3	1.61
4	55	12.7	2,398	8	4.00	4	2.00
5	32	7.4	1,257	9	8.59	6	5.76
6	15	3.5	525	4	9.15	3	6.86
7	14	3.2	520	7	16.15	5	11.53
8	12	2.8	317	7	26.53	6	22.74
Sum or Mean	434		19,017.7	56	3.53	32	2.02

[a]Blessed information-memory-concentration (test).

current address was 14.5 years. This stability was attributable to the inexpensive apartments provided by the New York City rent control program. The subjects reported the presence or history of disorders expected in an aging population: 65.0% reported arthritis; 49.3%, hypertension; 46.3%, shortness of breath; 39.9%, hearing loss; 39.7%, cataracts; 34.6%, ankle swelling; 26.7%, angina; 26.5%, cardiac rhythm irregularities; 21.3%, depression; 14.0%, myocardial infarction; 11.5%, diabetes; 10.2%, prior head injury; 6.8%, history of stroke or transient ischemic attack. Almost half (47.9%) were on diuretics, 24.5% on other antihypertensive drugs; 13.8% on digitalis; 13.0% on nitroglycerin; and 4.0% on antiarrhythmic drugs [3].

Development of Dementia

We report here the changes in mental status and the development of dementia in our cohort during 19,018 person-months or 1,585 person-years of follow-up (Table 1). During this period, 76 subjects had a change in mental status or clinical evidence of change in cognition or function and underwent the clinical evaluation for dementia. Fifteen of the subjects who underwent the clinical evaluation were considered to be nondemented. Three subjects had changes on the mental status test that proved to be reversible: one recovered from a right parietal infarct; one was depressed; and one was an alcoholic. One subject had an increase in mental status error score to 11, but remained functional on repeat evaluation. One subject with a known stroke and an IMC score of 3 developed functional impairment and was considered at risk for MID.

Fifty-six subjects met the criteria for diagnosis of dementia, 32 met diagnostic criteria for AD, 15 met diagnostic criteria for MID/MIX, 8 had other diagnoses, and 1 remained undiagnosed. The development of 56 cases of dementia during 1,585 person-years of follow-up may be restated as an incidence rate of 3.53 cases per 100 person-years at risk (0.0353/yr). A striking feature was that the number of cases of dementia was about the same as the number of heart attacks (50) in this same cohort during this time period and twice the number of cerebrovascular accidents (26).

Table 1 shows the incidence of dementia and AD as a function of entry mental status score. The degree of the relationship of the development of dementia and AD to the initial mental status score was unexpected. Two important conclusions could be drawn from these results. First, the 58.5% of the cohort with an initial mental status score of zero to two errors out of 33 possible errors was at low risk for developing dementia, AD in particular, the rate of which was less than 1 case per 100 person-years (0.01/yr). Individuals with error scores of 5 to 8 were at high risk for the development of dementia. Twenty-seven of the 73 subjects (37%) with an initial score of 5 to 8 developed a progressive dementia, suggesting that many of these individuals might have been in an early stage of dementia at intake, even though they still functioned normally. In this regard, we reviewed the initial functional evaluation of the 32 subjects who developed AD. On the functional rating scale, the distribution of the entry scores of the AD subjects did not differ significantly from the scores of those who did not develop dementia, and hence those subjects did not meet DSM-III criteria for dementia at entry. Initial mental status scores did not predict the MID/MIX rate, as was true for AD. Thus, MID/MIX occurred with an incidence rate of 0.85 per 100 person-years at risk, among the 71.2% of the initial cohort with mental status scores of 0 to 3. However, the incidence rate of MID/MIX rose to only 1.9 per 100 person-years at risk among those with initial scores of 5 to 8, as compared with an inci-

dence rate for AD of 11.9 per 100 person-years at risk.

Table 2 includes data on individual subjects who developed dementia classified by diagnosis. Characteristics present at the time of entrance into the study that distinguished the 32 subjects who developed AD from both the entire initial sample and from subjects who did not develop dementia were age, gender, and initial mental status scores. The 32 subjects developing AD were on average 80.8 years of age at intake into the study, about 1 year older than the entire cohort. Twenty-seven of the 32 (84.3%) were women, whereas 64.5% of all subjects in the entire cohort were women. The average initial error score on the mental status examination of the AD subjects was 5.18 compared with an average of 2.5 for the entire sample. We found, however, that a disproportionate number of those admitted to the study with mental status scores of 5 to 8 were women. We therefore carried out an analysis using a proportional hazard model to separate the effects of age, gender, and mental status on the development of dementia. The results, shown in Table 3, indicated that all three factors were independent predictors of dementia in our cohort, although the effect of gender was significant only at the $p = 0.08$ level.

The women with mental status scores of 5 to 8 had less education than the cohort as a whole. However, when years of education were included along with age, gender, and mental status in the proportional hazards model, education was not predictive of dementia. Yet within the 5 to 8 error score group, those with more education were more likely to become demented than their less-educated counterparts, but this effect was not statistically significant.

Table 4 compares selected risk factors in the AD and MID/MIX group with those in the nondemented group, which consisted of subjects who had neither dementia nor major cognitive changes as described above. In this table no significant positive risk factors for AD other than age can be identified; noteworthy are the low predictive values of history of head trauma, thyroid disease, and family history, factors that had previously been reported as significant risk factors for early-onset AD [1, 7, 13].

Because many of the "risk factor" measures vary in frequency according to gender, we compared the baseline findings in the women who developed AD to those in 245 women who had undergone at least one reevaluation and who did not develop dementia. In most respects, the subjects who developed AD were similar to those who did not; there was no significant difference in medical histories regarding anemia, angina, alcohol use, cancer, cardiac irregularity, depression, glaucoma, hearing loss, hip fracture, intermittent claudication, kidney disease, liver disease, rheumatic heart disease, seizures, or visual loss. Laboratory values including those for high-density lipoproteins were approximately the same. Self-ratings of happiness, social fulfillment, and satisfaction did not differ. Several factors appeared to indicate that the subjects who would develop AD were physically somewhat healthier: AD subjects were less likely to have (1) experienced diabetes, hypertension, or stroke (not significant by chi-square analysis); (2) smoked one pack of cigarettes or more per day; and (3) complained of shortness of breath. It should be noted that the risk factors that were reduced in the AD subjects may contribute to the occurrence of stroke and hence to classification of subjects with AD as MID/MIX. Four factors that have been reported as risk factors for AD did not predict the occurrence of AD in this cohort: family history of dementia (23% in the AD group vs 27% in the nondemented group); history of head injury (0% vs 8.4%); history of thyroid disease (7.7% vs 19.9%); and maternal age at time of subject's birth (25 vs 26 years). The women developing AD had an increased rate (not significant by chi-square analysis) of history of peptic ulcer, myocardial infarction, and cataract. Sinus bradycardia was more frequent in this group. A higher percentage of women developing AD was over 80 (78% vs 39%) at intake. Also, the women who developed AD had more memory complaints at intake than women who remained nondemented (22.2% vs 6.9%, $p < 0.02$).

The most important risk factor for MID/MIX was a history of prior stroke (46.7% compared with 3.4% in the nondemented group; chi-square, $p < 0.0001$). It should be noted, however, that a history of stroke is a weighted component of both the Hachinski and Rosen ischemic scores and hence plays a role in the diagnosis. Diabetes was present in 33.3% (5 of 15) of MID/MIX subjects, compared with 11.5% of the entire cohort; even with the small numbers in the MID/MIX group, this finding was significant (by chi-square analysis) at the $p < 0.03$ level. Hypertension per se was not a risk factor, but left ventricular hypertrophy, a marker of tissue changes that result from hypertension, was increased, although it was not statistically significant ($p = 0.1$). High-density lipoprotein levels were reduced in the male MID/MIX subjects (26 vs 37.6 mg/dl in all male subjects), but not in the female MID/MIX subjects (45 vs 45.8 mg/dl). Triglycerides at baseline were elevated in the MID/MIX subjects (170 ± 57 mg/dl in male MID/MIX subjects vs 138 in all male subjects; 217 ± 190 in female MID/MIX subjects vs 136 ± 78 in all female subjects) but the variability within groups was too great for this difference to be significant. Other lipids were unaltered in the MID/MIX subjects. There was no significant increase in angina or myocardial infarcts in the MID/MIX subjects. MID/MIX subjects, unlike AD subjects, were more likely to have a history of depression (chi-square, $p < 0.02$) and

Table 2. Subjects Who Developed Dementia; Changes in IMC Test Score

Diagnosis	Subject No.	Sex	Age at Intake (yr)	Hachinski Ischemic Score	IMC Test Score[a] B1	B2	B3	B4	B5	Note
AD	15	F	82	4	2	7	10	15	15	
AD	44	F	84	3	6	10	14	13	15	
AD	45	F	81	1	4	8	9	14	—	
AD	65	M	81	1	4	6	4	11	—	
AD	67	M	85	0	6	6	8	18	19	
AD	69	F	85	4	8	18	—	—	—	
AD	72	F	80	3	5	3	8	10	13	
AD	76	F	80	5	1	16	—	—	—	
AD	99	F	83	2	7	12	20	21	33	
AD	111	M	86	1	7	8	11	10	15	
AD	137	F	76	2	4	8	11	12	16	
AD	164	F	84	3	8	15	14	10	19	
AD	165	F	81	1	5	13	25	27	33	
AD	196	F	81	3	6	13	21	17	—	
AD	198	F	77	1	3	6	5	10	9	
AD	258	M	83	1	1	4	5	13	20	
AD	260	F	79	3	8	10	14	11	14	
AD	293	F	81	1	3	4	16	14	—	
AD	314	F	78	2	7	10	—	12	—	
AD	321	F	79	0	8	11	14	19	21	
AD	322	F	80	2	7	11	14	27	28	
AD	330	M	77	2	0	2	10	16	33	
AD	344	F	80	3	5	16	14	31	—	
AD	361	F	75	2	8	16	—	19	—	
AD	362	F	81	—	8	17	—	—	—	
AD	365	F	81	4	4	17	33	—	—	
AD	377	F	82	8	3	13	10	19	—	
AD	387	F	81	1	2	7	6	13	—	
AD	394	F	82	0	5	6	11	9	—	
AD	433	F	85	4	7	11	—	—	—	
AD	441	F	81	1	5	9	16	—	—	
AD	488	F	76	1	5	4	7	—	—	
Average[b]			80.8	2.2 ± 1.7	5.1 ± 2.3	(N = 32)				
MID/MIX	007	M	83	5	8	5	17	—	—	
MID/MIX	033	M	75	9	4	4	7	10	14	
MID/MIX	046	F	79	4	3	9	—	—	—	
MID/MIX	098	F	82	5	7	8	19	16	12	
MID/MIX	132	F	86	10	0	1	3	—	—	
MID/MIX	163	F	85	8	2	4	6	15	18	
MID/MIX	168	F	83	7	3	8	16	23	—	
MID/MIX	173	F	75	8	1	3	3	9	—	
MID/MIX	193	F	74	9	4	8	8	17	—	
MID/MIX	202	F	79	8	4	17	—	—	—	
MID/MIX	261	F	77	9	5	3	5	12	—	
MID/MIX	282	M	84	8	2	6	10	10	—	
MID/MIX	288	F	82	6	6	13	—	—	—	
MID/MIX	297	M	80	10	2	11	14	21	—	
MID/MIX	417	M	81	7	3	11	—	—	—	
Average[b]			80.3	7.5 ± 1.9	3.6 ±2.2	(N = 15)				
Other	006	F	84	—	2	—	18	22	—	
Other	008	M	82	1	3	3	1	9	—	Metabolic encephalopathy
Other	075	M	79	0	3	11	12	10	—	Alcoholic
Other	126	F	81	2	5	6	6	10	8	B_{12} < 100 pg/ml
Other	128	F	77	9	1	17	—	—	—	Astrocytoma
Other	131	F	83	3	5	3	2	7	9	? Parkinson's disease, ? NPH
Other	313	M	79	3	7	5	7	11	9	Uncertain diagnosis
Other	320	M	80	2	2	2	12	—	—	Alcoholic
Other	398	M	83	—	4	8	5	16	—	B_{12} < 100 pg/ml
Average[b]			80.9	2.9 ± 2.9	3.6 ± 1.9	(N = 9)				

[a]B1–B5 are successive (approximately annual) IMC test scores.
[b]Averages of ischemic score and B1 IMC test score are expressed plus or minus standard deviation.

IMC = Blessed information-memory-concentration (test); AD = Alzheimer's disease; MID/MIX = multiinfarct dementia/mixed AD and cerebrovascular disease; NPH = normal-pressure hydrocephalus; — = evaluation not done.

Table 3. Effects of Age, Gender, and Baseline IMC Test Score (No. of Errors) on the Incidence of Total Dementia Estimated Using a Proportional Hazard Model: Bronx Aging Study 1980–1985[a]

Predictor Variable	Beta (β)	Standard Error (β)	Significance (*p*)	Rate Ratio[b] (RR)	95 Percent Confidence Limits (RR)
Age	0.17	0.04	0.0002	5.5	2.5–11.9
Gender (F/M)	0.54	0.31	0.0812	1.7	0.93–3.2
Baseline score					
0–2	—	—	—	1.0	—
3–4	+ 0.13	0.20	0.5194	1.1	0.8–1.7
5–8	+ 1.04	0.18	< 0.0001	2.8	1.9–4.0

[a]N = 422.
[b]The rate ratio is the estimated incidence rate for one group (e.g., women) divided by the corresponding rate for a comparison group (e.g., men). It is computed for a dichotomous variable by taking the natural antilog of beta. Each estimated rate ratio is adjusted for all other predictors in the model.

IMC = Blessed information-memory-concentration (test).

Table 4. Risk Factor/Morbid Conditions at Initial Evaluation

	Nondemented Group (N = 350)[a]	AD Group (N = 32)	MID/MIX Group (N = 15)
Female (%)	61.4	84.4	66.7
History (%)			
Smoking			
Current	10.9	0.0	13.3
Past	51.1	28.1	40.0
Thyroid disease	13.4	9.4	20.0
Head trauma	10.0	3.1	20.0
Depression	22.0	28.1	26.7
Cancer	12.0	9.4	6.7
Diabetes	11.1	6.3	33.3
Hypertension	52.3	40.6	33.3
Angina	26.0	18.8	33.3
History of CVA	3.4	0.0	46.7
CVA	4.9	0.0 Before diagnosis 12.5 After diagnosis	20.0 Before diagnosis 26.7 After diagnosis
History of MI	11.1	15.6	20.0
MI	14.6	0.0 Before diagnosis 9.4 After diagnosis	6.7 Before diagnosis 20.0 After diagnosis
Pacemaker	2.3	3.1	6.7
Laboratory test values			
LVH (%)	12.6	6.3	20.0
Sinus bradycardia (24-hr Holter monitor)	27.4	25.0	20.0
Thyroxine (meq/dl)	7.4 ± 1.6	7.6 ± 1.6	7.3 ± 1.9
B_{12} (pg/ml)	530.0 ± 367.4	597.5 ± 327.4	524.0 ± 171.9
HDL (mg/dl)	43.3 ± 13.5	44.6 ± 10.4	35.1 ± 12.8

[a]The nondemented group excluded the patients with cognitive change who did not meet DSM-III criteria for dementia, as well as those with clinical diagnoses of dementia.

AD = Alzheimer's disease; MID/MIX = multiinfarct dementia/mixed AD and cerebrovascular disease; MI = myocardial infarction; CVA = cerebrovascular accident; LVH = left ventricular hypertrophy; HDL = high-density lipoproteins.

scored lower than nondemented subjects on self-ratings of satisfaction and health. Because of the relatively small number of subjects with MID/MIX, other important risk factors may not have become evident.

Discussion

Both prevalence [9, 23] and incidence [12, 27] of dementia rise sharply with age, with the majority of cases being attributable to AD. The incidence of dementia of 3.5 per 100 person-years for an 80-year-old cohort fell well within the range of values reported by Hagnell and colleagues [12] in the Lundby study and by Sluss and colleagues [27] in the Baltimore longitudinal study. The rate ratio of women to men developing dementia in our sample was greater than that reported in other series [4, 12, 25]. Twenty-seven of the 32 (84.4%) who developed AD in our study were women, whereas women constituted just under two-thirds of the entire sample. In the Hagnell study [12],

the total incidence of dementia was somewhat higher for men past 80 (4.4%) than women (3.2%), although there was no breakdown by diagnosis. The incidence of 2.0 per 100 person-years at risk for AD at age 80 was between the values of 3.2% reported by Sluss and colleagues [27] and 1.3% reported by Sayetta [26].

The incidence of AD reported in Table 2, which was based upon cases meeting diagnostic criteria, was undoubtedly an underestimate. The true incidence of AD was clouded by our inability to diagnose it accurately in patients with coexisting MID/MIX or other neurodegenerative disorders that mask its presence. Based upon the data from Tomlinson and colleagues [29] and Rosen and colleagues [24] and clinical considerations, one could estimate that about 7 of the MID/MIX subjects and 3 of the subjects with diagnoses other than MID/MIX or AD may have had coexistent AD. Thus, the number of cases of AD might have been as high as 43, which would correspond to a total incidence of AD of 2.6 per 100 person-years at risk, a figure that could serve as a reasonable upper limit in this series.

The extent to which mental status test scores predicted dementia was noteworthy. Roth [25] found little success in diagnosing the early stages of dementia. For example, of the 711 persons 65 years or older in the Newcastle-upon-Tyne study, 30 people were observed to develop dementia during a 2- to 4-year follow-up. Only 6 of the 30 were suspected of having organic mental disorders on the initial examination. Jarvik and Blum [14] found the scores on the vocabulary, similarities, and digit-symbol subtests of the Wechsler Adult Intelligence Scale (WAIS) obtained 20 years previously predictive of which elderly (mean age 84 years) persons would be diagnosed as demented or nondemented. In our study, the scores on the WAIS vocabulary and similarities test achieved at the initial evaluation did not predict who would subsequently become demented.

Three aspects of the relationship of AD to the baseline mental status score deserve emphasis. The first is that 60% of this 80-year-old cohort had less than a 0.5% per year risk of developing AD. Thus, there is a substantial segment of the elderly population that will likely remain free of this "geriatric tragedy" at least in the immediate future.

A second aspect to be emphasized is the usefulness of mental status tests in general, and the Blessed IMC test in particular, in identifying cognitive impairment. Mental status tests were developed to test deficits resulting from generalized disease of the brain, in contrast to tests for focal lesions, such as aphasia batteries. Our study has established that such tests are valid for identifying the beginning of cognitive impairment in still-functioning elderly persons. Families are capable of ignoring or denying early symptoms and, in our sample, the mental status test often detected change before the families did. Nevertheless, the mental status tests by themselves are not specific, and the need for additional early diagnostic indicators is evident.

More than 90% of those who scored over five errors on the IMC test at intake made errors in all or part of the five-point memory phrase question. These individuals were then functioning individuals with memory impairment and might well have been considered to have "benign senescent forgetfulness." The finding that 37% of these subjects developed dementia raises a question as to the usefulness of Kral's [20] concept of benign senescent forgetfulness.

Clinically, AD patients may experience depression, especially if they become aware of their progressive cognitive deficit. In our study, we have documented that depression does not usually occur at the earliest phase of the disorder. In contrast, several of the MID/MIX patients were initially depressed, a finding consistent with the inclusion of depression in the Hachinski ischemic score [11].

At this stage of the prospective study, the ability to identify risk factors for AD is limited by the number of subjects in each group. We would expect to be able only to identify factors with a "relative" risk greater than 3.0 for factors present in more than 10% of the initial sample. The two significant risk factors for AD confirmed by this study are age and gender. A history of dementia in a first-degree relative is an important risk factor in younger patients [13], but not in our cohort. The rates of two recently reported risk factors for AD, a history of head injury [1, 13, 22] and a history of thyroid disease [13], are sufficiently lower in our AD subjects than in our nondemented subjects to make it unlikely that these would become risk factors, even if the number of AD subjects were doubled. Because case control studies reporting these risk factors were carried out on subjects under 70 years old, one could speculate that these particular factors are more important in the so-called presenile AD patient than in the elderly patient.

It has become evident in this study that a majority of apparently mentally intact 80-year-olds are, indeed, at a low risk for the onset of dementia, but that there is also a significant minority at high risk. Moreover, in this study population the incidence of dementia exceeded that of stroke and equaled that of presumed heart attacks. Thus, as success continues in the prevention of cardiovascular and cerebrovascular disease, dementia—AD in particular—will become the most serious health problem of the aged.

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