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Journal

Neurology, 54(11)

ISSN

0028-3878

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Publication Date

2000-06-13

DOI

10.1212/wnl.54.11.2072

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Peer reviewed

Age-specific incidence rates of Alzheimer's disease

The Baltimore Longitudinal Study of Aging

C. Kawas, MD; S. Gray, PhD; R. Brookmeyer, PhD; J. Fozard, PhD; and A. Zonderman, PhD

Article abstract—*Objective:* To estimate age-specific incidence rates of AD in the Baltimore Longitudinal Study of Aging (BLSA). *Background:* The BLSA is a volunteer cohort of normal subjects followed longitudinally with biennial evaluations at the Gerontology Research Center of the National Institute on Aging. *Methods:* Subjects are 1236 participants (802 men, 434 women) in the BLSA with longitudinal follow-up between January 1985 and May 1998. The average length of follow-up was 7.5 years, with participants evaluated every 2 years by physical, neurologic, and neuropsychological examinations. Using Diagnostic and Statistical Manual of Mental Disorders, 3rd ed., revised and National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria, the authors diagnosed dementia and AD. *Results:* The authors diagnosed 155 cases of dementia, of which 114 (74%) were AD. Incidence rates of AD increased with age from an estimated 0.08% per year (95% CI 0.00 to 0.43) in the 60 to 65 age group to an estimated 6.48% per year (95% CI 5.01 to 8.38) in the 85+ age group for men and women combined. The doubling time of incidence rates was estimated to be approximately 4.4 years and the median time of conversion from mild cognitive impairment to diagnosis of AD was estimated to be 4.4 years. There was a trend for women to have higher incidence rates than men and for fewer years of education to be associated with higher incidence rates; however, these effects were not significant. *Conclusion:* Incidence rates for AD in the BLSA are consistent with published rates in other studies. The longitudinally followed subjects of the BLSA offer a unique opportunity to prospectively investigate the antecedents of AD. **Key words:** AD—Incidence—Incidence rates—Dementia.

NEUROLOGY 2000;54:2072–2077

In the United States, the majority of senile dementia cases are attributed to AD.¹ Estimates of AD incidence rates and the effects of demographic variables on those rates are necessary for our basic understanding of AD and are useful in formulating hypotheses about disease etiology. In addition, although most studies of risk factors in AD have used prevalent cases of AD, the examination of risk (and protective) factors in incident cases provides a more reliable means of identifying factors relevant to the development of the disorder.

For the last 15 years, we have been following the participants of the Baltimore Longitudinal Study of Aging (BLSA), a volunteer cohort followed by the National Institute on Aging. The objective of this article is to describe our methods of ascertainment, report incidence rates of AD and dementia observed in the BLSA between calendar years 1985 and 1998, and assess the effects of demographic variables such as age and gender on those rates.

Methods. *Subjects.* The BLSA was initiated in 1958 to study prospectively the effects of normal aging.² Followed

by the Intramural Research Program of the National Institute on Aging, the cohort consists of community-dwelling volunteers who are predominantly white (90.3%), of upper-middle socioeconomic status, and with an above average educational level. Initially limited to men, enrollment of women began in 1978. To date, 2476 subjects (1566 men, 910 women) have been enrolled in the BLSA.

This report uses data collected on all BLSA participants ($n = 1236$; 802 men, 434 women) who had some or all of their longitudinal follow-up at age 55 or older between January 1985 and May 1998. When the dataset was closed for this analysis, 2476 participants had been enrolled in the BLSA, but approximately half of the subjects had all of their follow-up before January 1, 1985, or were younger than the age of interest (<55 years old). Of the remaining subjects, we were unable to ascertain outcome on only two. Table 1 summarizes the demographic information on study participants. Participants who continued to return every 2 years to the Gerontology Research Center for 2.5 days of multidisciplinary evaluations were considered active. Participants who did not visit the center in 3 years were considered inactive, and were generally evaluated in their

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Supported in part by NIH/NIA grants AG08325/Risk Factors and Early Signs in Alzheimer's Disease, AG05146/Alzheimer's Disease Research Center, and M01 RR02719/General Clinical Research Center at Johns Hopkins Bayview Medical Center.

Received November 2, 1999. Accepted in final form February 16, 2000.

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Table 1 Demographic characteristics of BLSA incidence study participants

Variable	Men, n (%)	Women, n (%)
Age at beginning of follow-up,* y		
55–64	324 (40.4)	170 (39.2)
65–74	249 (31.0)	144 (33.2)
75–84	187 (23.3)	106 (24.4)
85–97	42 (5.2)	14 (3.2)
Education, y†		
4–12	69 (8.6)	57 (13.1)
13–16	279 (34.8)	192 (44.2)
17–25	453 (56.6)	185 (42.6)
Length of follow-up, y		
0–4	209 (26.1)	119 (27.4)
5–9	379 (47.3)	182 (41.9)
10–13	214 (26.7)	133 (30.6)
Total	802	434

* January 1, 1985, for participants entering the Baltimore Longitudinal Study of Aging (BLSA) on or before January 1, 1985, and date of first visit for participants entering the BLSA after January 1, 1985.

† One male participant missing education variable.

homes or local healthcare facilities. At the beginning of follow-up (i.e., January 1, 1985, for participants entering the BLSA on or before January 1, 1985, and date of first visit for participants entering the BLSA after January 1, 1985), 1006 (81.4%) of the participants were active and 230 (18.6%) were inactive.

Detection of incident dementia cases. Case detection for all subjects consisted of in-person examination and appropriate laboratory and imaging studies whenever possible, as well as informant and medical record information. Procedural flow charts by study status (active and inactive) are shown in figure 1 and are described below.

Active participant procedures. Active participants older than 65 years had neurologic examinations and neuropsychological testing in addition to the usual BLSA pro-

cedures.² Neuropsychological testing included the Blessed Information-Memory-Concentration (BIMC) test,³ Mini-Mental State Examination,⁴ Immediate and Delayed Cued Recall,⁵ Boston Naming Test,⁶ Controlled Verbal Fluency,⁷ Trail Making Tests A and B,⁸ Clock Drawing⁹ and other constructions,¹⁰ Center for Epidemiologic Studies Depression Scale,¹¹ Pfeffer Functional Activities Questionnaire,¹² and National Adult Reading Test.¹³ Participants who made three or more errors on the BIMC test received additional laboratory testing (including blood chemistries, CT or MRI scans, or EEG, if indicated) and the Dementia Questionnaire (DQ).¹⁴

Active participants age 55 to 64 were first screened with the BIMC test. Those with three or more errors on the BIMC test were also examined clinically and administered the above procedures.

Inactive participant procedures. Inactive participants 55 years of age or older (or nearest family member) were initially contacted by telephone. Participants were screened with the Telephone BIMC (TIMC) test,¹⁵ and the DQ was administered to family informants. Participants with three or more errors on the TIMC test or with reported cognitive decline received home visits consisting of neurologic examination and neuropsychological testing and medical records were obtained. CT scans and laboratory workup were performed in subjects who met criteria for dementia. Of those participants with two or fewer errors on the TIMC test, a 15% age-stratified random sample received home visits.

Consensus diagnostic conferences and criteria. In a consensus diagnostic conference, information from all sources was reviewed to establish diagnoses for the incidence study. Subjects with progressive cognitive impairment (including loss of memory and at least one other area of cognition) of sufficient severity to interfere with social or occupational functioning were classified as having dementia (Diagnostic and Statistical Manual of Mental Disorders, 3rd ed., revised [DSM-III-R]).¹⁶ If subjects were determined to have cognitive decline but did not meet criteria for dementia, they were classified as suspected/possible early dementia.

BLSA participants with a diagnosis of dementia were further classified by diagnostic category with use of National

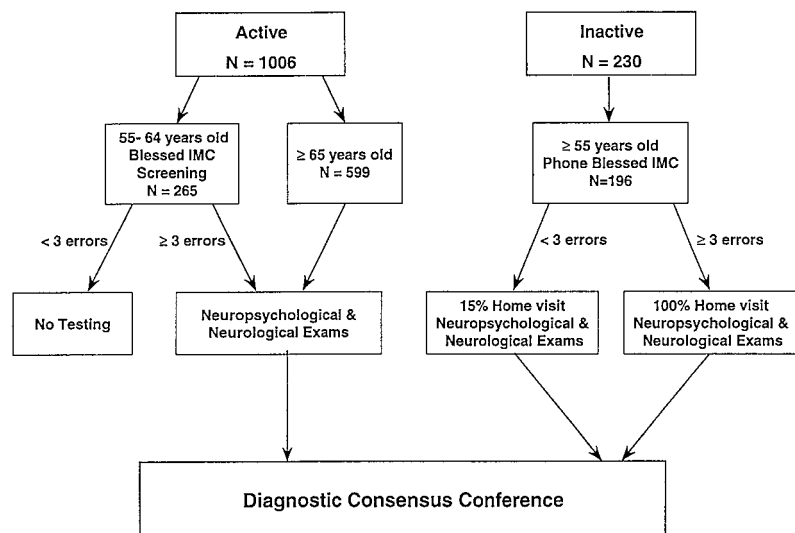


Figure 1. Procedural flow charts by study status. IMC = Information-Memory-Concentration.

Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association¹⁷ criteria for definite, probable, and possible AD. An additional designation was used for participants who met clinical criteria for probable AD but did not complete neuroimaging studies. These subjects were categorized as consistent with AD.

Demented subjects with evidence of significant cerebrovascular disease by history, examination, or imaging were designated as vascular or mixed vascular/AD dementia. All subjects in this category had modified Hachinski ischemic scores of greater than 4.¹⁸ Date of diagnosis was defined as the year in which the subject met DSM-III-R criteria for dementia. At the time we began our studies, there were no widely accepted criteria for vascular dementia. In 1992, we retrospectively applied the criteria proposed by the State of California AD Diagnostic and Treatment Centers.¹⁹ All subjects designated as having vascular dementia met criteria for probable or possible vascular dementia.

Statistical analysis. AD incidence rates were computed for 5-year age intervals by using a person-years analysis.²⁰ Subjects were considered to be at risk and contributed person-years from study entry until date of diagnosis of AD or other dementia, date of last contact, or date of death. For each 5-year age group, a 95% CI for the incidence rate was computed assuming a Poisson distribution for the number of new cases in each age group.

To obtain a smooth age-specific incidence curve, logistic regression analysis was used.²¹ For each year of age, the number of subjects reaching that age who were disease-free and, of those, the number who developed AD within that year were calculated. The log odds of developing AD was then modeled as a function of age. From the resulting model, the predicted age-specific probability of developing AD (incidence) was calculated. The effects of gender and education on incidence were assessed by fitting additional logistic regression models that included both age and the demographic variables.

We also estimated the median conversion time from the first reported sign of cognitive impairment to the diagnosis of AD. Disease onset was determined by asking informants for the year in which the first symptom, usually memory

Table 3 Age- and gender-specific incidence rates for AD in the Baltimore Longitudinal Study of Aging

Age interval, y	Person-years	No. of new AD cases	Incidence rate (% per year)	95% CI
Men				
55–59	609.6	0	0.00	(0.00, 0.61)
60–64	885.5	0	0.00	(0.00, 0.42)
65–69	1055.8	1	0.09	(0.00, 0.53)
70–74	1082.2	6	0.55	(0.20, 1.21)
75–79	937.6	7	0.75	(0.30, 1.54)
80–84	799.2	10	1.25	(0.60, 2.30)
85+	597.1	43	7.20	(5.21, 9.70)
Total (55+)	5967.0	67	1.12	(0.87, 1.43)
Women				
55–59	352.5	0	0.00	(0.00, 1.05)
60–64	404.8	1	0.25	(0.01, 1.38)
65–69	465.0	1	0.22	(0.01, 1.20)
70–74	580.5	1	0.17	(0.00, 0.96)
75–79	635.7	7	1.10	(0.44, 2.27)
80–84	498.3	18	3.61	(2.14, 5.71)
85+	360.2	19	5.27	(3.18, 8.24)
Total (55+)	3296.9	47	1.43	(1.05, 1.90)
Men and women combined				
55–59	962.1	0	0.00	(0.00, 0.38)
60–64	1290.3	1	0.08	(0.00, 0.43)
65–69	1520.9	2	0.13	(0.02, 0.48)
70–74	1662.6	7	0.42	(0.17, 0.87)
75–79	1573.3	14	0.89	(0.49, 1.49)
80–84	1297.5	28	2.16	(1.43, 3.12)
85+	957.2	62	6.48	(4.97, 8.30)
Total (55+)	9263.9	114	1.23	(1.02, 1.48)

Table 2 Diagnostic classification: 155 incident cases of dementia in the Baltimore Longitudinal Study of Aging (1985–1998)

Diagnosis	No. (%) of cases
AD	
Definite	1 (0.6)
Probable	71 (45.8)
Possible	28 (18.1)
History consistent with AD	14 (9.0)
Mixed/multi-infarct dementia	16 (10.3)
Parkinson’s with dementia	11 (7.1)
Dementia/other*	4 (2.5)
Dementia unspecified	10 (6.5)
Total	155 (100)

* Dementia/other = multiple system atrophy, head injury, variable cognitive performance likely due to depression, normal pressure hydrocephalus.

loss, was noticed by any family member, friend, or physician. This analysis included BLSA participants 55 years or older between January 1985 and May 1998. A Kaplan-Meier curve was used to estimate the distribution of conversion times, where participants who did not meet AD criteria during follow-up were considered censored at date of diagnosis of other dementia, date of last contact, or date of death.

Results. Overall, 155 incident cases of dementia were identified among BLSA participants over approximately a 13-year period (1985 through 1998). Of these, 65.8% of cases were active BLSA participants at the time diagnostic criteria were met, and 34.8% were inactive. AD accounted for 114 (74%) of the dementia cases during this time interval, and mixed/multi-infarct dementia accounted for the next largest percentage (10.3%) of dementia cases. Table 2 shows the distribution of identified cases by diagnostic category. An additional 125 participants were classified as suspected/possible early dementia. These subjects did not meet DSM-III-R criteria for dementia but were noted to have changes in memory or other cognitive domains.

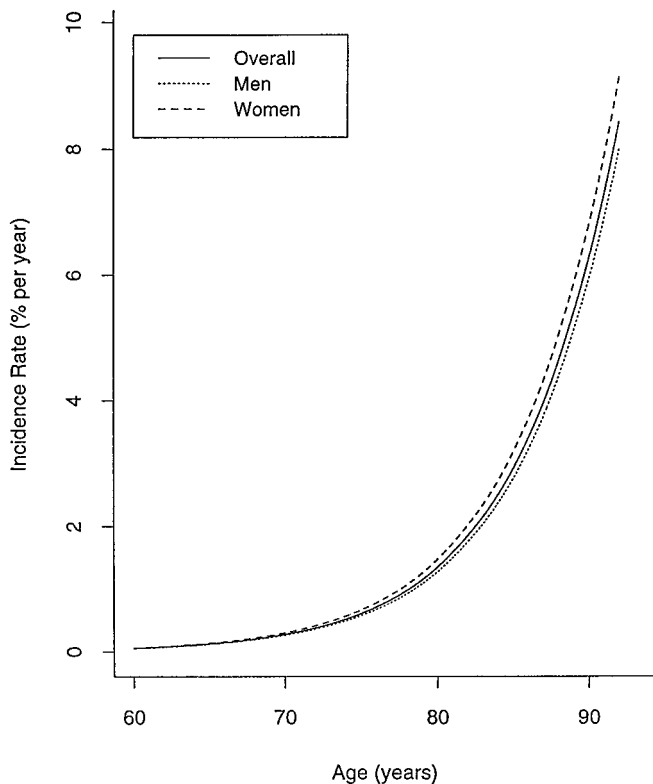


Figure 2. Age-specific incidence rates of AD (in percent per year) observed in the Baltimore Longitudinal Study of Aging, January 1985–May 1998.

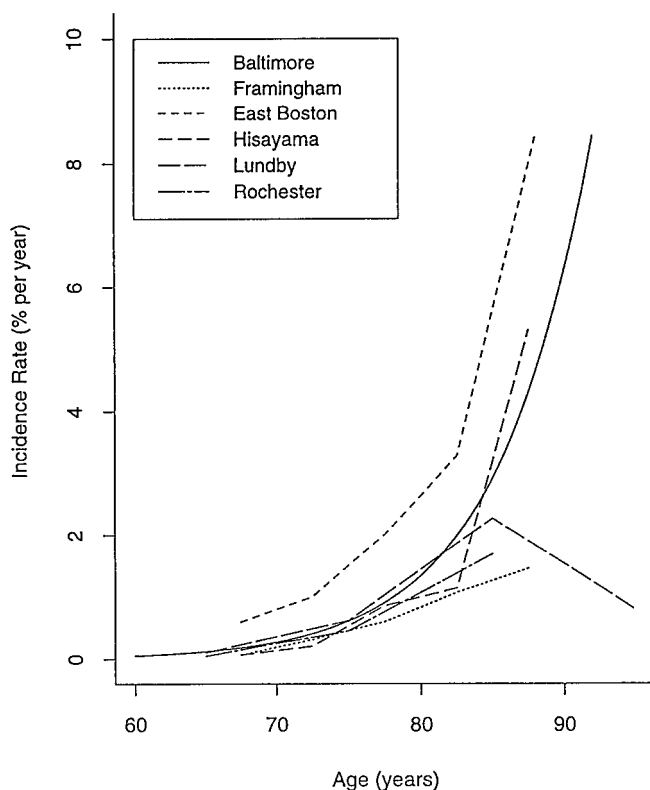


Figure 3. Age-specific incidence rates of AD in selected studies.

During this study period, 9264 person-years (age 55+) accrued, resulting in an observed crude incidence rate of dementia of 1.67% per year (95% CI 1.42 to 1.96%) and a crude incidence rate of AD of 1.23% per year (95% CI 1.02 to 1.48%). Table 3 shows the estimated age- and gender-specific incidence rates for AD in the BLSA. Overall, the incidence rates for AD increased with age from an estimated 0.08% per year in the 60 to 65 age group to an estimated 6.48% per year in the 85+ age group.

Using logistic regression analysis, we obtained an estimated smooth age-specific incidence curve for AD (figure 2). From that analysis, the probability of developing AD was found to increase significantly with age ($p < 0.01$). The effect of age on the probability of developing AD was linear on the log odds scale. From figure 2, we estimated

the time for the incidence rate to double to be approximately 4.4 years. This appears consistent with the estimates obtained from the person-year analysis.

There was a trend for women to have higher incidence rates than men, and for fewer years of education to be associated with higher incidence rates (table 4). Specifically, the odds of developing AD was estimated to be 10% higher for women than for men when participants of similar age and education were compared ($p = 0.65$). The odds of developing AD was estimated to be 27% less for participants with some college education (13 to 16 years of education) and 36% less for participants with some graduate school education (17 to 25 years of education) compared to those with an education of high school or less (4 to 12 years of education) of the same age and gender ($p = 0.34$ and 0.16, respectively). Neither the effects of gender nor education, however, were significant.

Between January 1985 and May 1998, 254 BLSA participants were identified as having onset of mild cognitive impairment at an age greater than or equal to 55. Using these participants, we estimated the median conversion time from onset of mild cognitive impairment to diagnosis of AD to be 4.4 years, and the time for 25% and 75% of the participants to meet AD criteria to be 2.3 and 7.4 years.

Table 4 Estimated odds ratios for AD by gender and education

Variable	OR (95% CI)	<i>p</i> Value
Gender*		
Men	1.00 —	—
Women	1.10 (0.74, 1.62)	0.65
Education,† y		
4–12	1.00 —	—
13–16	0.73 (0.39, 1.39)	0.34
17–25	0.64 (0.34, 1.19)	0.16

* Comparing groups of similar age and education.

† Comparing groups of similar age and gender.

Discussion. Published estimates of AD incidence rates have been variable. Population differences as well as differences in methodology, for case ascertainment as well as other aspects of the study, may account for much of this variability.²² Although the BLSA is a select cohort with an unusually high level

of education, the estimated incidence rates largely fall in the middle of the spectrum when compared with other studies²³⁻²⁹ (figure 3).

In this study, there was a trend for women to be at higher risk of AD, but this did not reach significance. Many of the studies that have found women to be at higher risk for developing AD have detected the effect at the older age ranges³⁰⁻³³ where we had limited statistical power. Similarly, we had limited ability to study education as a risk factor for AD because the cohort is relatively homogeneous with regard to education. Nonetheless, we detected a trend for less education to be associated with higher risk, in keeping with other published studies.³⁴⁻³⁶

The BLSA is a volunteer cohort. Caution must be used when trying to generalize findings from select cohorts to broader populations, but the identification of dementia and AD cases in the BLSA allows the investigation of prospectively collected data for up to 40 years before the development of AD. Rarely have so many subjects been studied so intensely and for such a long period. Moreover, identification of cases in the BLSA provides *incident* cases of AD for studies of risk and protective factors, thereby avoiding the potential biases of investigations in prevalent cases where identification of factors may be more related to length of disease or detection biases. Furthermore, we have used diagnostic procedures that are comparable to those of other studies, and these procedures provide classification of subjects for our already published investigations of estrogen and nonsteroidal anti-inflammatory drugs in risk of AD^{37,38} and for studies we anticipate in the future. The extraordinary variety of data and the advantages of prospective (premorbid) data collection make use of the BLSA cohort a unique opportunity for the study of aging and dementia.

Acknowledgment

The authors thank the BLSA participants and the Intramural Scientists of the NIA who made this work possible. The authors also thank Dr. Pamela Talalay for her editorial guidance and Ms. Paula David for assistance in the preparation of this manuscript.

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TNF gene polymorphism and its relation to intracerebral production of $TNF\alpha$ and $TNF\beta$ in AD

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Article abstract—*Objective:* To analyze the extent of tumor necrosis factor- α ($TNF\alpha$) and $TNF\beta$ gene polymorphism in patients with AD and to relate it to intrathecal levels of these cytokines. *Methods:* Analyses of $TNF\alpha$ and $TNF\beta$ gene polymorphism were performed using PCR in 52 patients with AD and in 25 control subjects, and the levels of corresponding cytokines were analyzed using ELISA. *Results:* Patients with AD displayed significantly higher intrathecal levels of $TNF\alpha$, but not $TNF\beta$, compared with the control subjects. The levels of these cytokines did not differ significantly in patients displaying different alleles of the *TNF* gene. *Conclusions:* Results indicate that increased intrathecal production of $TNF\alpha$ in AD is preferentially controlled by environmental stimuli rather than genetic makeup. **Key words:** AD—Tumor necrosis factor- α —Tumor necrosis factor- β —Gene polymorphism.

NEUROLOGY 2000;54:2077–2081

AD is characterized by atrophy of the brain subsequent to neuronal and synaptic degeneration, decreased dendritic arborization, and formation of neurofibrillary tangles and senile plaques (SP). A protein of 42 amino acid length, with a high tendency to aggregate, called β -amyloid protein ($A\beta$), has been identified as the major component of SP.¹ $A\beta$ is derived from a 90 to 140-kDa precursor called amyloid precursor protein (APP).² The cause of AD and reasons for its progressive course are unknown, but involvement of the immune system in the pathogenesis has been discussed for years. For example, $CD4^+$ and $CD8^+$ T lymphocytes are present in affected AD brain tissue.³ In addition, reactive microglial cells have been demonstrated to express class II molecules of the major histocompatibility complex and Fc receptors.⁴ Thus, all the appropriate elements necessary for an immune response are present lo-

cally in the brain of AD patients. Both activated microglia and T lymphocytes can be a source of cytokine production.⁵ Indeed, interleukin (IL)-1, IL-6, and tumor necrosis factor- α ($TNF\alpha$) were detected in postmortem analyses of AD brains.^{6–8} These cytokines may be involved in the pathogenesis of AD (e.g., by promoting local inflammatory responses).⁹ IL-1 has also been demonstrated to enhance the synthesis of APP messenger RNA (mRNA) in human endothelial cells,¹⁰ suggesting a direct role for this cytokine in the formation of SP. Interestingly, the IL-1 receptor antagonist occurring naturally in the brain,¹¹ and blocking interaction of IL-1 with its receptor,¹² displays neuroprotective properties with respect to ischemic and excitotoxic brain damage in experimental rat models.¹³ Furthermore, $TNF\alpha$ —a powerful cytokine that induces apoptosis in the extraneural compartments of the body—has been dem-

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Supported by grants from the Göteborg Medical Society, University of Göteborg, The Swedish Association against Rheumatism, King Gustaf V's 80-year Foundation, Stroke Foundation, Gamla Tjänarinnor Foundation, John and Brit Wennerströms Foundation, Rune and Ulla Amlöv Foundation, Konrad and Helfrid Johanssons Foundation, Loo and Hans Ostermans Foundation, Clas Groschinsky Foundation, Wilhelm and Martina Lundgrens Foundation, Alzheimer's Foundation, the Swedish Association of Neurologically Disabled, the Swedish Heart, Lung Foundation, the Swedish society of Medicine, and the Swedish Medical Research Council (grant nos. 11560 and 12103).

Received June 11, 1999. Accepted in final form February 25, 2000.

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