Dietary Links to Alzheimer's Disease

William B. Grant

803 Marlbank Drive, Yorktown, VA 23692-4353

Summary

Recent findings that elderly African-Americans and Japanese living in the United States have much higher prevalence of Alzheimer's disease (6.24% and 4.1%, respectively) than those still living in their ethnic homelands (<2%) suggested that environmental rather than genetic factors are the primary agents causing Alzheimer's disease. Recent papers linking clinical expression of Alzheimer's disease to oxidative stress and cerebral infarct suggest that diet is a key factor in the development of Alzheimer's disease. To test this hypothesis, regression analyses were performed on the prevalence of Alzheimer's disease in the 65+ age population for 11 countries obtained from 18 community-wide studies versus components of the national diets. The primary findings are that fat and total caloric supply have the highest correlations with Alzheimer's disease prevalence rates (r^2 = 0.932 and 0.880, respectively). In addition, fish consumption is found to reduce the prevalence of Alzheimer's disease in the European and North American countries. The literature suggests that fat contributes to oxidative stress and inflammation and that fish oils combat inflammation. Recent papers finding that several dietary components and supplements have been found effective in delaying the onset of Alzheimer's disease, including antioxidants, fish, and nonsteroidal anti-inflammatory drugs are consistent with this finding.

Key words caloric intake, fat, fish oil, inflammation, nutrition, oxidative stress

Alzheimer's disease (AD) is a common type of dementia or decline in intellectual function first described by A. Alzheimer [1907]. Some of the characteristics include intraneuronal fibrillary tangles, diffuse, neuritic and burned-out plaques and neuronal loss [Harman, 1995; Lippa et al., 1996].

Epidemiological studies have not identified causal factors for Alzheimer's disease as seen in a number of reviews [Heyman et al., 1984; Mortimer and Hutton, 1985; Rocca et al., 1986; Schoenberg, 1986; Broe et al., 1990; Beard et al., 1992; Breteler et al., 1992; White, 1992; Disterhoft et al., 1994; Katzman and Kawas, 1994; Prince et al., 1994; Keefover, 1996; van Duijn, 1996]. However, recently several orally ingested substances have been found to delay the onset or progression of AD: estrogen [Tang et al., 1996b]; non-steroidal antiinflammatory drugs (NSAIDs) [Stewart et al., 1997]; and vitamin E [Sano et al., 1997].

In the 1980s, one of the common hypotheses for the cause of AD was exposure to environmental aluminium. Aluminium is well known to have neurotoxic properties [Bolla et al., 1992; Martin, 1994]. Many studies have shown associations between elevated exposure to aluminum and Alzheimer's disease prevalence [e.g., Doll, 1993; Forbes and McLachlan, 1996]. Savory et al. [1996] reviewed the controversy surrounding the role of aluminium in AD, and suggested six basic questions which would have to be addressed to resolve the issue. Thus, while aluminum may not cause AD in and of itself, it seems to be associated with AD often enough that it may be involved in the development of AD.

Genetic factors play a role in the development of AD, especially in early-onset (familial) AD, which accounts for 5-10% of all AD [Prince et al., 1994; Farlow et al., 1994; Breitner and Welsh, 1995; Harman, 1995; Fox et al., 1996; Gridley, 1996; Levy-Lahad and Bird, 1996; Selkoe, 1996; Tang et al., 1996a; van Duijn, 1996; Blacker et al., 1997; Lendon et al., 1997], but also late-onset (sporadic) AD, where apolipoprotein-e4 allele is a known risk factor [Davis et al., 1997]. (See Lippa et al. [1996] for a comparison of the two types of AD.) However, while genetic factors may increase the risk of developing AD, there is no genetic model which can account for the geographical distribution of AD prevalence, and a number of recent papers have conceded that both environmental and genetic factors may be involved in AD [e.g., Lippa et al., 1996; Martin and Kukull, 1996; Evans et al., 1997; Morrison-Bogorad et al., 1997].

Recent papers published on African-Americans in Indianapolis [Hendrie et al., 1995] and on Japanese living in the state of Washington [Graves et al., 1996] and Honolulu [White et al., 1996] reported these groups had much higher AD prevalence rates than those still living in their ethnic homelands. For the African-Americans, the AD prevalence

Address correspondence to: Dr. William B. Grant, 803 Marlbank Drive, Yorktown, VA 23692-4353 Email: wbgrant@norfolk.infi.net

Alzheimer's Disease Review (ISSN 1093-5355) is published by the Sanders-Brown Center on Aging, University of Kentucky. It is available online at: http://www.coa.uky.edu/ADReview/.

Table 1. Alzheimer's disease and senile dementia studies used in the statistical analysis. Taiwan is included in the table, but not used in the analysis

Location	AD (%)	SD (%)	Year	Reference
Canada	5.1*	6.74	1992	Lindsay et al., 1994
China				
Beijing	0.7*	3.2	1986	Li et al., 1989
Beijing	1.8*	3.2	1986	Kua, 1991
Beijing	1.1*	3.56	1989	Shen et al., 1994
Europe				
Finland	3.6*	6.7	1977-81	Sulkava et al., 1985
Appignano, Italy	3.9	6.3	1987	Rocca et al., 1990
Zaragoza, Spain	4.1*		1987	Lobo et al., 1990
Stockholm, Sweden	3.2*	6.1	1987	Fratiglioni et al., 1991
Japan				
Japan	2.4	5.8	1983	Shibayama et al., 1986
Kanagawa	1.8*	4.6	1983?	Hasegawa et al., 1986
Miki town	1.8		1986?	Fukunishi et al., 1991
Hisayama	1.5	6.7	1985	Ueda et al., 1992
Nigeria	1.4*	2.29	1993	Hendrie et al., 1995
Singapore	1.9*	2.8	1985	Kua, 1991
Taiwan				
Rural Taiwan	2.6	2.7	1983	Lin et al., 1984
Taipei	0.6	1.7	1987	Rin et al., 1987
Taiwan	1.2	2.0	1988-89	Liu et al., 1995
Taiwan	2.3	2.8	1992	Liu et al., 1994, 1995
United Kingdom				
Cambridge	4.4*	7.7	1985	O'Connor et al., 1990
USA				
Honolulu, HI	4.7*	7.6/10.3	1992	White et al., 1996
Indianapolis, IN	6.24*	8.24	1993	Hendrie et al., 1995
King County, WA	3.5*	6.3	1993	Graves et al., 1996

* adjusted using the U.S. age distribution (65-74 years - 60%, 75-84 years - 30%, 85+ years - 10%) in the original text or in this work.

rate for individuals over 65 years old was 6.24%, while for Africans living in Ibadan, Nigeria, the rate was 1.41% [Hendrie et al., 1995]. For Japanese living in Washington, the AD prevalence was 3.5%, while for Japanese men living in Honolulu, the prevalence rate was 4.7%. The two Japanese studies average to give 4.1%; the average of four studies of AD prevalence rate in Japan was 1.88% (see Table 1). These findings suggest that the prevalence of AD is more strongly influenced by diet and nutrition, environment, and/or lifestyle, than by genetics.

There is a large body of literature on life extension [e.g., Pearson and Shaw, 1982; Walford, 1986; Harman, 1994; Walford and Walford, 1994; Barnard, 1995; Hayflick, 1996; Hitchcox, 1996 and references therein]. Most of this literature stresses the importance of caloric restriction, as well as proper nutrition. Much of this work is based on the idea that oxidative stress is the major cause of lifespan shortening. Harman wrote his seminal paper on this topic in 1956 [Harman, 1956].

Recent studies discuss the role of oxidative stress in AD. Several reports [e.g., Clausen, 1984; Harman, 1994, 1995; Smith and Perry, 1995; Butterfield, 1996; Hensley et al., 1996; Smith et al., 1996a, 1997a,b] suggest that oxidative stress is linked to AD. In addition, the studies by Hulette et al. [1997 and Snowdon et al. [1997] indicated that clinical expression of AD is facilitated by cerebral infarction or stroke. Since the risk of stroke is generally enhanced by such dietary factors as high fat consumption and trace mineral imbalance [Carper, 1993; Shinton et al. 1995], this finding provided further impetus to the present study.

Meta-analysis of community-based epidemiological studies of Alzheimer's disease prevalence

In order to examine the possible role of diet in the incidence and prevalence of AD, the meta-analysis approach [Hunt, 1997] on epidemiological community-based studies with respect to the diet of the country near the time of the study was chosen. A survey of the literature on AD failed to find any detailed consideration of what the relationship might be between diet with respect to the community-based studies of AD prevalence rates. Several researchers had proposed cross-cultural studies as way to study the causes of AD [e.g., Jorm, 1991; Osuntokun et al. 1992; White, 1992]. The reports by Hendrie et al. [1995] and White et al. [1996] discussed above are outgrowths of those suggestions.

The decision on which studies to include and which to omit was carefully considered. Of the more than one hundred studies of the community rate of dementia [see the reviews in: Rocca et al., 1986; Schoenberg et al., 1986; Shibayama, et al., 1986; Jorm et al., 1987; Jorm, 1991; Bachman et al., 1992; Hébert and Brayne, 1995; Liu et al., 1995; Keefover, 1996], only 18 passed tests enabling them to be included in the analysis presented in this paper. The tests included: 1 - that the 65+ age AD prevalence rate was given or could be calculated from the data presented. If only undifferentiated dementia prevalence rates were given, the study was not included because it is too difficult to determine the fraction who have AD [e.g., Breteler et al., 1992; Hébert and Brayne, 1995; Liu et al., 1995]; 2 - that those living in the community as well as those living in institutions be included in the study; 3 - that the studies be conducted after 1979 for two reasons: a - people with AD are living longer now, due to better medical care [Beard et al., 1992]; and b - the protocols for determining who in the community has AD changed in 1980 with the adoption of the DSM-III standard test [Am. Psychiatr. Assoc., 1980]; and 4 - that the dietary factors for the country can be readily determined. Those studies included are shown in Table 1, which includes the AD prevalence rate, the year of the study, and the reference.

Since the incidence of AD increases with a 5.1-year doubling time for AD [Jorm et al., 1987], and since the lifespan in some of the developing countries is several years lower than in the U.S., it is important that the age-adjusted AD prevalence data

be normalized in the same manner. The easiest approach is to use the U.S. age distribution of those over 65 (65-74, 60%; 75-84, 30%; 85+, 10%; Riggs [1996]). This has been done for the AD prevalence data designated with an asterisk. The original data for three studies in Japan were not available, but since the life expectancy there in 1992 was 79 years versus 76 years in the U.S. [Wright, 1995] that shouldn't matter. The same can be said about Finland, where the life expectancy was also 76 years.

There is some question regarding the AD prevalence rate determined for Nigeria, even though the data by Hendrie et al. [1995] were age-adjusted to the age distribution in the U.S. The mortality rates for those with AD in Nigeria are higher than those elsewhere because of poorer treatment for such other diseases as bronchopneumonia. Thus, the reported 1.4% prevalence is probably low when survival after developing AD is considered. On the other hand, Osuntokun et al. [1992] earlier reported no AD in Nigeria. The discrepancy between the two studies may be in the fact that one was an urban, the other a rural population study. A parallel situation can be found in the study of rheumatoid arthritis (RA) prevalence. Rural Africans have very low prevalence while urban Africans and African Americans have much higher RA prevalence [Silman et al., 1993]. Thus, the discrepancy between the two Nigerian studies may well be due to different diets in urban and rural regions. For this study, the value of 1.4% will be used, with the presumed lower prevalence in rural areas balancing the lower life expectancy after developing AD.

Some well-known studies were not included in the analysis because they did not satisfy the criteria used in this study. For example, the East Boston study [Evans et al., 1989] measured the prevalence of AD only for people living in the community, and has been criticized for classifying nearly all cases of dementia as probable senile dementia of the Alzheimer's type (SDAT) when most studies in the developed countries find a value more like 50-60% of AD cases belonging to the SDAT category [Jorm, 1991; Bachman et al., 1992; Graves et al., 1996]. The Framingham, Ma. Study [Bachman et al., 1992] screened out people who had a stroke or heart problem prior to consideration. The Shanghai study [Zhang et al., 1990] sampled only noninstitutionalized community residents.

Having said this, there is still the question of whether the meta-analysis approach with data from diverse countries is appropriate for AD because of differences in methodology, life expectancies, genetic differences, confounding variables etc. The strongest reason for affirming this approach is that three studies comparing the AD prevalence rates for people with the same ethnic background living in the U.S. and in their native land showed such marked differences. Hendrie et al. [1995] showed that African-Americans living in Indianapolis had a 6.24% AD prevalence versus 1.4% for Africans living in Ibadan, Nigeria. Graves et al. [1996] found 3.5% AD prevalence for Japanese living in the state of Washington, while White et al. [1996] found that Japanese men living in Hawaii had a 4.7% AD prevalence. These two results are in sharp contrast to four studies showing that Japanese living in Japan had a mean AD prevalence of 1.88% in the mid-1980s. While commenting on some of the methodological problems encountered in doing cross-cultural studies such as White's, Martin and Kukull [1996] could not find any fundamental problem with them.

In order to satisfy the requirement that the data points used be independent, values for each country were averaged if the total caloric supply was nearly the same for each AD prevalence determination. This step reduced the number of data points to 11. The data for Taiwan are included in Table 1 to support the finding of low AD prevalence rates for other parts of southeast Asia, as well as the idea that community-based AD prevalence rate determinations can be reasonably consistent. However, they are not used in the meta-analysis because dietary data for Taiwan are not available.

The Japanese-American and African-American values were combined to give an AD prevalence value for the U.S. as a whole. The AD prevalence values for Japanese-Americans are probably lower than for most other Americans for two reasons: 1 - men generally have lower AD prevalence than women; and 2 - Japanese living in the United States convert slowly from the traditional Japanese diet to the standard American diet [Tillotson et al., 1973]. On the other hand, the AD prevalence for African Americans are probably higher than for other Americans. Heyman et al. [1991] showed that blacks in the North Carolina Piedmont region have more prevalence of chronic degenerative diseases (CDDs) that are traditionally linked to diet than do Caucasians, suggesting that they have diets more prone to cause such CDDs. The two Japanese-American studies were combined into one value, then averaged with the African-American value to yield an AD prevalence value for the U.S. of $5.17 \pm 1.07\%$.

Since both AD and non-AD senile dementia (SD) now seem to be affected by cerebral infarcts [Hulette et al., 1997; Snowdon et al., 1997], it seemed likely that they might have the same dietary links. Thus, the rates for total prevalence of SD, which includes AD, are also included in the meta-analysis for those studies used in the AD meta-analysis.

For diet/nutrition, the *Food Balance Sheets* published by The Food and Agriculture Organization (FAO) of the United Nations [FAO, 1991] is used. The FAO regularly publishes a detailed summary of total caloric supply, as well as for many components of the diet for 145 countries as they

Table 2. Dietary per capita supply values used in the correlation analysis from 4 years prior to the AD prevalence studies.

Country	Year	Total food (cal)	Fat (g)	Fish (cal.)	Cereals (cal.)
Canada	1988	3451	152	33	705
China	1983	2550	36.5	11	1826
Finland	1976	3130	133	50	728
Italy	1983	3485	133	29	1124
Japan	1981	2797	76.5	175	1235
Nigeria	1988	2230	42.4	8	934
Singapore	1981	2720	75	54	1038
Spain	1983	3360	142.5	50	823
Sweden	1987	3030	131	63	628
UK	1981	3200	136	23	655
USA	1988	3658	163.5	26	718

Table 3. Regression coefficients (r), coefficients of determination (r^2), F, and significance (p) between components of the diet and Alzheimer's disease and senile dementia for community-based studies for the 65+ age population.

Component	r	r^2	F	p
Alzheimer's disease (N=11)				
fat	0.966	0.932	124.1	<0.001
total food	0.938	0.88	65.7	<0.001
%cereals	-0.831	0.69	20.1	0.002
%cereals (China deleted)	-0.876	0.768	26.5	<0.001
Senile dementia (N=10)				
fat	0.908	0.825	37.8	<0.001
total food	0.886	0.785	29.2	<0.001
% cereals	-0.728	0.53	9.0	0.017
%cereals (China deleted)	-0.772	0.596	10.3	0.015

existed in the mid-1980s. The values represent food available to the consumer, and do not take into account losses due to spoilage, wastage etc. Thus, they overestimate the amount actually consumed. The most recent edition has information in three-year periods from 1961-1988. However, this is the only way to make international comparisons, and the loss factors may be similar for different countries. These values can be considered and index of consumption. U.S. Dept. of Commerce [1994] was used to extend the U.S. data base to 1992, and Wright [1995] was used to extend the Nigerian data base to 1992. The dietary values used in the analysis presented in this paper are given in Table 2. Values for components not found to be significant are omitted for simplicity.

The analysis presented here uses the caloric or fat supply for the period approximately 4 years prior to the study. To determine the optimal period to use, regressions were run on a 11-country data set for 1-2 year periods ranging from the study to 8 years after the start, and in coarser intervals out to 15 years prior to the study. The regressions for total caloric supply peaked for the period 3-4 years prior to the study, while that for fat peaked in the year of the study. Similar results were obtained from the Rochester, Minnesota, longitudinal study, discussed below. Diets do change with time (most of the countries have increasing caloric supply for the 5 years prior to the study period, but some have little change, and some actually have declining caloric supply). The dietary values 4 years prior to the study were used in most of the analysis, since it seems reasonable that prevalence data would be most strongly affected no more recently than about half the average remaining lifetime for those diagnosed with AD. The current half-life for such people is about 4-6 years in the U.S. [Beard et al., 1994; Stern et al., 1997], although it may be lower in other countries where medical care might not be as intensive.

To determine the most important variables relating to the prevalence of AD, multiple linear regressions were run with two or more dietary components and the significance factors, p, for each component were noted. Only total fat supply and total caloric supply had consistently low values. Part of the reason that some of the other components did not have high significance is likely due to the fact that they are relatively minor fractions of the diet. However, they may still play roles in the development of AD, as will be discussed later. Cereals were also found to have a significant inverse correlation with AD prevalence.

The statistical findings for fat supply, total food supply, and cereals for both AD and SD are given in Table 3. Fat has the highest correlation with both AD and SD prevalence [see, also, Kalmijn et al., 1997]. Regression analyses for total senile dementia give similar findings to those for AD, but are somewhat weaker. There is more spread in the data about the regression line. This probably arises from the fact that the criteria for determining who has senile dementia, which is based in part on the severity, varies from study to study. The tests for SD do not seem to be as rigorously defined as for AD, as shown, for example, by the two values given in the study by White et al. [1996].

A plot of the AD prevalence vs. fat is shown in Figure 1. The analysis for fat shows a threshold of 6.5 grams and a slope of 0.312%/10 g of fat. Further details are found in Table 3.

A plot of the AD prevalence vs. total caloric supply is shown in Figure 2 for the 11-country data set. From this analysis, the threshold determined for prevalence is 2000 calories, and the slope is 0.309% per 100 calories above the threshold. The high correlation between total caloric supply and AD prevalence is probably due to the fact that many of the concentrated foods found in high-caloric diets lead to acidic digestive systems and free radical production.

A significant inverse correlation was found between the fraction of calories derived from cereals and AD prevalence. While whole grains have antioxidant vitamins and minerals, it is not clear that the cereals generally consumed are

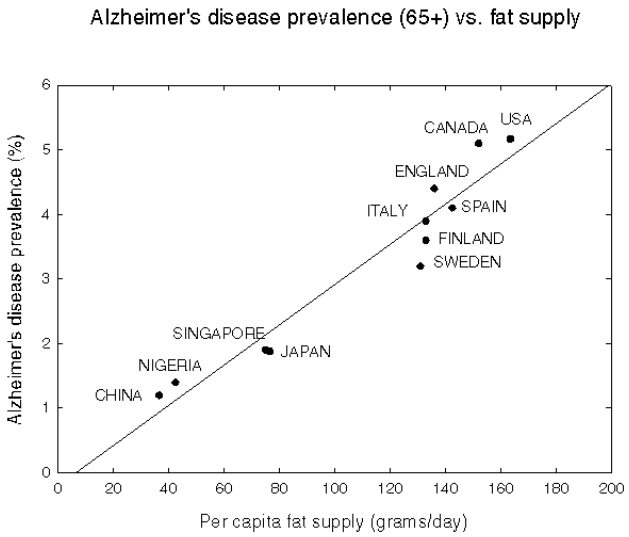

Figure 1. Scatter plot of Alzheimer's disease prevalence versus fat supply for 11 countries, along with the linear regression fit to the data (AD prevalence rate = -0.203+(0.0312*fat (grams/day))).

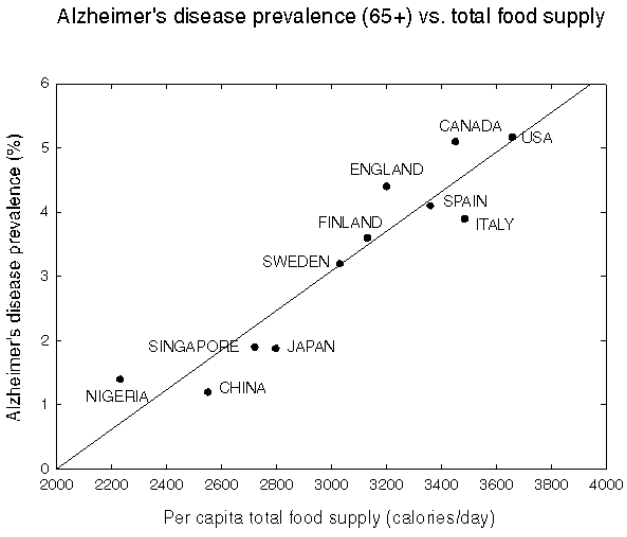

Figure 2. Scatter plot of Alzheimer's disease prevalence versus total food supply for 11 countries, along with the linear regression fit to the data (AD prevalence rate = -6.178 + (0.00309*(total calories/day))).

whole grains. The correlation is likely to arise from the fact that countries with low fat supply have high cereals supply, rather than any direct therapeutic effect of the cereals. This point should be investigated in greater depth.

While these results seem reasonable, there is the concern that the Asian and African countries have enough differences with respect to European and North American countries, such as age distribution, life expectancy after developing AD, genetic differences, vastly different diets, different physical exertion norms etc., that they may skew the results. While one normally keeps all data in a meta-analysis unless there is a very good reason to exclude it, it seemed worthwhile to redo the statistical analysis on the European/North American subset of the data. The results of doing so are given in Table 4. What is found is that fat is still highly associated with AD, but total calories decrease in association and significance. Cereals drop to an insignificant association. Fish, however, become almost significant at the 95% confidence level for an inverse association. When a multiple linear regression is run with fat and fish, the highest association and significance is achieved. The equation for AD prevalence as a function of fat and fish for the 7-country study is AD prevalence = - 1.009 + 0.0425*fat (grams/day) - 0.0203* fish (calories/day). In other words, 1 calorie of fish counters the effects of 0.48 grams of fat or approximately 4.3 calories of fat.

Table 4. Regression coefficients (r), coefficients of determination (r2), F, and significance (p) between components of the diet and Alzheimer's disease for 7 European and North American countries for the 65+ age population.

Component	r	r^2	F	p
fat	0.894	0.8	20	0.007
total calories	0.789	0.623	8.3	0.035
fish	-0.746	0.556	6.3	0.054
% cereals	-0.353	0.125	0.125	0.437
fat + fish	0.968	0.937	29.9	0.004

Thus, for relatively genetically homogeneous populations with similar diets, somewhat different statistical associations are found. This analysis adds further support to the 11-country analysis and other studies [e.g., Harman, 1995, 1996; Smith et al., 1997a; Kalmijn et al., 1997; Sano et al., 1997] on the likely role of fat in being highly associated with AD, and to the findings by Kalmijn et al. [1997] that fish in the diet reduces the expression of cognitive impairment and Stewart et al. [1997] that inflammation is involved. The lower significance of calories in the diet is also consistent with the recent finding by Rexrode et al. [1997] that obesity per se is not correlated with hemorrhagic stroke.

Fish and fish oil

Kalmijn et al. [1997] showed that increasing fish in the diet reduced the risk of developing dementia, while linoleic acid increased it. Kim et al. [1995] showed that fish oil (eicosapentaenoic acid (EPA; n-3)) may reduce the amount of adhesion in the blood, while Harris [1997] showed that fish oil reduces blood triacylglycerol, and that plant-derived n-3 fatty acid is not equivalent to marine-based acids in its effect on humans.

Alzheimer's disease incidence study

Additional support for total caloric supply and fat directly affecting AD rates comes from the Rochester, Minnesota, longitudinal study [Kokmen et al., 1996a]. Figure 1 in that

work gives the AD incidence rate for 10-year age ranges for five 5-year periods from 1960 to 1984. The values can be converted to incidence rates for those over the age of 65 by assuming the U.S. population distribution [Riggs, 1996]. Doing so results in the values given in Table 5. Average U.S. total food supply for the periods are taken from FAO [1991] and U.S. Dept. of Commerce [1975]. When the total daily per capita caloric supply from the period of the study is used, a regression analysis yields an r^2 value of 0.75, with p = 0.06. However, when the total caloric supply for the previous five-year period is used, r^2 jumps to 0.91, and p decreases to 0.012. For fat, the r^2 for the current period is 0.65, with p=0.100, while for the previous period, $r^2 = 0.89$ with p=0.016. Based on the dietary values in the U.S. in the late 1950s, 3190 calories and 137 g of fat, the estimated AD prevalence in the early 1960s are 3.7% based on calories and 4.1% based on fat. These results should be considered supporting evidence for the role of both total caloric and fat supply in the incidence/prevalence of AD, and that the older one becomes, the more important it is to reduce fat and calories in the diet.

Cross-correlation of AD with other chronic degenerative diseases

Additional support for the roles of fat and total caloric supply in causing AD can be found by investigating the cross correlations between dementia and other diseases. For this, the prevalence rates for males and females of all ages for the 8 major geopolitical regions of the world are used [Murray and Lopez, 1996a]. The dementia data (Table 6) are primarily due to AD, although other degenerative and hereditary central nervous system disorders are also included. Using the data for all ages in Murray and Lopez [1996a] overcomes the problem of age distributions in the various countries and regions since age is essentially normalized out of the analysis, i.e., if a disease affects primarily older people, it should exist at high rates only in regions with relatively high proportions of older people. Over 30 diseases and causes of death were examined in this regard. The infectious diseases were not included in the analysis. Twenty one were found to have statistically-significant ($p<0.05$) correlations with dementia for at least one sex, while 16 were found to be significant for both sexes, if applicable. Those not found to be statistically significant include cancers of the cervix, liver, and stomach, which are likely caused by either behavior or specific components of the diet [Weisburger and Williams, 1995]. Those for which high correlations were found are listed in Table 6, along with current thinking on the causes of the disease. The probable causes for most of the diseases include animal fat, total fat, total caloric consumption, low fiber consumption, salt, and smoking. It appears that the diet is the primary cause of all of these diseases, and that which particular disease each person develops depends to some extent on his own genetic makeup.

Table 5. Alzheimer's disease incidence rates, age-adjusted for the 65+ population from the Rochester, Minnesota longitudinal study [Kokmen et al., 1996], along with average U.S. total food supply levels for those periods.

		Average U.S.	
Years	**AD incidence rate***	**total food (cal) ****	**total fat (g)**
1955-1959		3200	138.5
1960-1964	1.99	3211	140.4
1965-1969	1.71	3300	146.9
1970-1974	2.24	3392	152.6
1975-1979	3.21	3453	154.3
1980-1984	3.17	3517	160.9

* per 100,000 person years

****** FAO[1991] and U.S. Dept. of Commerce [1975], mid-period

Alzheimer's disease prevalence in the US

A value of 5.1% AD prevalence for those 65 or older in the U.S. can be determined based on a combination of the regression relationships for 166 g of fat in 1992 (4.97$\pm$0.40%), the total per capita food supply level of about 3700 calories in 1992 (5.26$\pm$0.53%), and the three most recent U.S. community-based AD prevalence studies [Hendrie et al., 1995; Graves et al., 1996; White et al., 1996] (5.17$\pm$1.07%). These average to 5.1$\pm$0.6%. Based on the age distribution of the U.S. population 65+ in 1994 [U.S. Bureau of the Census, 1996], this corresponds to a 0.87$\pm$0.10% probability of having AD at the age of 65, with the probability increasing (decreasing) by a factor of 1.146 for each additional (fewer) year(s) of age [Jorm, 1987]. This gives 1.7$\pm$0.2 million victims of AD 65 years and older, and 0.4$\pm$0.1 million under 65 years of age, or a total of 2.1$\pm$0.3 million in the U.S. in 1994. From the analysis in this paper, another 1.1 million are thought have other forms of senile dementia.

Mechanisms whereby body chemistry is altered by diet

Given the statistical findings that fat and total caloric supply are highly associated with both incidence and prevalence of AD, it is interesting to examine the literature on the effects of both fat and high caloric consumption on body chemistry. First, both fat and high total-caloric consumption lead to the presence of more free radicals in the body. Fat easily oxidizes to generate free radicals, and free radicals are a natural by product of nutrient processing in the mitochondria. While a certain amount of free radicals are useful in the body, too many, such as found in a high-fat, high-caloric-consumption diet, are harmful, since they lead to more rapid aging [e.g., Harman, 1994, 1995] and many CDDs [e.g., Harman, 1996]. Diets which produce an acid digestive system lead to the removal from the body of base

Table 6. Cross correlations between prevalence of dementia (primarily Alzheimer's disease, but includes other degenerative and hereditary CNS disorders) and other chronic degenerative diseases. The disease data are taken from Murray and Lopez [1996a].

Disease	Male		Female		Association	Reference
	r^2	p	r^2	p		
Appendicitis	0.43	0.076	0.73	0.007	animal products	Grant [submitted]
Brain						
Parkinson's disease	0.88	<0.001	0.94	<0.001	oxidative stress	Fahn and Cohen [1992]
					calories, animal fat	Logroscino et al. [1996]
Schizophrenia*	0.89	0.005	0.87	0.006	fat	Christensen and Christensen [1988]
Stroke	0.84	0.001	0.91	<0.001	salt, alcohol, animal fats	Carper [1993]
						Shinton et al. [1995]
Cancer						
bladder	0.83	0.002	0.91	0.003	smoking	Weisburger [1990]
breast			0.84	0.001	fat	Wynder et al. [1986]; Carroll et al. [1987]
					animal fat	Rose et al. [1986]
colorectal	0.92	<0.001	0.95	<0.001	animal fat	Rose et al. [1986]
					calories, fat, low fiber	Reddy [1993]
corpus uteri			0.81	0.002	meat, fat, alcohol?	Carper [1993]
leukemia	0.91	<0.001	0.82	0.002	calories	Hursting et al. [1993]
lymphomas and multiple myeloma	0.76	0.005	0.72	0.008	weakened immune system	Morra and Potts [1994]
melanoma	0.8	0.003	0.85	0.001	UV-B, fat	Carper [1993]
ovarian			0.93	<0.001	fat	Calvert et al. [1987]
pancreatic	0.89	<0.001	0.94	<0.001	smoking, fat	Weisburger [1990]
					smoking, diet?	Ahlgren [1996]
prostate	0.66	0.014			calories, fat	Surgeon General [1988]
					animal fat	Rose et al. [1986]
trachea, bronchia, lung	0.86	<0.001	0.87	<0.001	smoking, fat	Zhao et al. [1991]
Diabetes mellitus (cases)	0.46	0.066	0.67	0.015	fat, calories, stress	Norris et al. [1995]
Heart						
acute myocardial infarction	0.56	0.034	0.63	0.019	smoking, hypertension, obesity, saturated fats, salt	Norris et al. [1995]
angina pectoris	0.52	0.043	0.49	0.055	calories, smoking, stress	Norris et al. [1995]
congestive heart failure	0.5	0.049	0.38	0.11	sodium	Norris et al. [1995]
Rheumatoid arthritis	0.6	0.024	0.95	<0.001	diet, fish oil**	Darlington and Gamlin [1996]
Stomach						
peptic ulcer	0.4	0.095	0.59	0.026	infection, use of NSAIDs, pathologic hypersecretory states, alcohol?, tobacco?, aging	Norris et al. [1995]

* missing data for Latin America and the Caribbean and the Middle Eastern crescent
** inverse association

cations or alkali metals, such as calcium, magnesium, and potassium, which try to neutralize the acid situation, as well as increased absorption of transition metal ions, which normally exist in the oxidized state. For example, diets high in proteins are known to cause both low absorption of dietary calcium and the leaching out of calcium from the bones [Lutz, 1984; Hegsted, 1986; Metz et al., 1993]. Acid drinks also deplete the body's store of base cations [Massey and Whiting, 1993]. Sodium chloride also reduces body base cations [Nordin et al., 1993]. Refined carbohydrates have similar effects [Wade, 1992]. For example, bread made with white flour contains phytate which reduces the absorption of alkali metal ions [Reinhold, 1971; Wills, 1973]. Diets high in proteins, fats, and refined carbohydrates are generally low in fresh fruits and vegetables and complex carbohydrates, which are good sources of antioxidants such as vitamin C and selenium, as well as essential trace minerals [Ames et al., 1993]. Salonen et al. [1988] found an inverse correlation between blood pressure and serum antioxidants vitamins C and selenium. Tea contains antioxidants [Weisburger, 1996] and may be effective in lowering AD prevalence rates. However, the countries included in the meta-

analysis which have low AD prevalence generally have values consistent with other dietary factors, so no conclusion regarding the efficacy of tea can be reached.

Vegetarian diets generally lead to a higher potassium/sodium ratio than do omnivore diets [Rouse et al., 1984]. This leads to higher calcium retention [Lemann et al., 1993].

The acid digestive condition from such diets also promotes the absorption of transition metal ions (e.g., cobalt, iron, and mercury), which normally exist in an inert oxidized state, but can be dissolved in strong acids [Weberg and Berstad, 1986; Martin, 1994; Aisen and Davis, 1997]. Transition metal ions in the mitochondria can catalyze free radical reactions [e.g., Quagliano and Vallarino, 1969; Stadtman, 1992; Smith and Perry, 1995], thereby enhancing the production of free radicals from the fats and other foods ingested.

Trace minerals and Alzheimer's disease

There are many reports of the association of elevated levels of aluminum, transition metal atoms, as well as sodium and chloride in the brains of people who died with AD [Ehmann et al., 1986; Thompson et al., 1988; Wenstrup et al., 1990; Markesbery and Ehmann, 1994; Savory et al., 1996], while alkali metal ions tend to be in lower abundance [Thompson et al., 1988; Markesbery and Ehmann, 1994]. Table 7 gives a summary of the ratios of the trace elements in the autopsied brains of those with AD to the controls, averaged from several studies [Ehmann et al., 1986; Thompson et al., 1988; Wenstrup et al., 1990]. The data from the hippocampus were used from the Thompson et al. study. Four of the transition metal ions have ratios from 1.15 to 1.40, while mercury, a component of silver amalgam fillings, has a ratio of 1.85. Sodium from table salt has a ratio of 1.14, indicating that people with AD probably have diets elevated in salt compared to the rest of the population. The alkali metal ion ratios vary from 0.69 to 0.84, and are thus as much depressed as the transition metals are enhanced. While the functions of the alkali metals in normally-functioning brains is not understood, there is evidence that rubidium, for example, does play a role, due to its usual ratio with respect to other elements [Markesbery and Ehmann, 1994]. Such heavy ions can function as free-radical traps. The nonmetal, selenium, is relatively unchanged from people with AD to the controls. These results are quite consistent with the notion that a high-acid-forming, high-sodium diet depletes the body of essential trace minerals while increasing the absorption of transition metal ions, thus contributing to the risk of developing AD.

Table 7. Ratios of trace metals in the brains of those who died with AD compared to controls.

Element	Ratio
Transition metals	
Silver (Ag)	1.4
Cobalt (Co)	1.4
Iron (Fe)	1.15
Mercury (Hg)	1.85
Scandium (Sc)	1.22
Alkali metals	
Cesium (Cs)	0.83
Potassium (K)	0.84
Rubidium (Rb)	0.69
Sodium (Na)	1.14
Nonmetal	
Selenium (Se)	0.98

Oxidative stress and Alzheimer's disease

The diet-influenced body chemistries associated with the high-caloric, high-fat diets are themselves linked to the onset and progression of AD through oxidative stress. Reactive oxygen species (ROS), which include both oxygen-derived free radicals and other oxygen compounds such as hydrogen peroxide, can be produced in the body by oxidation in the metabolism of food. Transition metals can reduce hydrogen peroxide to the highly reactive hydroxyl radical [Aisen and Davis, 1997]. ROS are especially abundant in diets high in overheated fats and oils often found in fried foods [Pitchford, 1993], as well as in high-caloric diets [Harman, 1995, 1996]. In addition, beta-amyloid peptide in the brain can generate free radicals [Butterfield, 1996; Smith et al., 1996a]. A number of aging processes involving ROS leading to AD and SD have been identified [Pearson and Shaw, 1982]: mutagenesis, leading to plaque formation in arteries; T-cell immune failure, leading to the development of atherosclerotic plaques by failing to destroy them; cross-linking of molecules in arterial walls, leading to hypertension or high blood pressure; abnormal clotting due to organic peroxide-induced deficiency of the natural anti-clotting hormone prostocyclin in the artery lining; strokes; and direct destruction of neurons [see, also, Butterfield, 1996; Hensley et al., 1996; Smith et al., 1996a]. The ROS can be neutralized in the body by antioxidants such as vitamins C and E, which, however, also have the potential to increase the amounts of reduced forms of transition metal ions, thereby increasing oxidative damage [Smith et al., 1996a]. Oxidative stress is also associated with Parkinson's disease [Logroscino et al., 1996], where both total caloric and fat consumption were shown to be highly correlated with Parkinson's disease in case studies. Advanced glycation end products (AGEs) can generate ROS, and are linked to the development of diabetic and other vascular diseases [Yan et al., 1994; Smith et al., 1996b; Finch and Cohen, 1997].

Inflammation

Inflammation also arises from prostaglandins derived from fatty acids [Erasmus, 1993]. Series 1 prostaglandins (PGE1), derived from linolenic acid with linoleic acid as the start-

ing point, decrease inflammation response. Series 2 prostaglandins (PGE2), derived from arachidonic acid found in meats and other animal products, as well as from linoleic acid, lead to salt retention by the kidneys, leading to high blood pressure, and cause inflammation. Series 3 prostaglandins, derived from EPA found in fish oils, prevent arachidonic acid from being released from membranes, thus preventing PGE2 formation. Thus, fats seem to play a major role in the development of inflammation. AGEs are also involved in inflammation in the brain [Yan et al., 1997]. NSAIDs, which reduce inflammation, are effective in reducing the risk of developing AD [Aisen and Davis, 1997; Stewart et al., 1997].

Causality

High correlations do not themselves necessarily imply causality; other confounding factors may be involved which are not included in the analysis. Hill [1965] laid out the criteria by which the claim of causality can be evaluated in biological systems. These criteria include strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy. For causality to exist, not all of the criteria have to be satisfied. However, the more that are satisfied, the more likely that causality exists. Renton [1994] reviewed the relation between epidemiological studies and public health policy decisions and concluded that epidemiological studies must be integrated with biological science.

The primary criteria for causality are listed and evaluated for high-fat-, high-total-caloric-consumption diets as the primary cause of sporadic AD and SD. By primary cause, it is meant that the more fat or calories are ingested, the greater the risk of developing AD and SD, and that the risk from diet is greater than the risk from other factors. It is acknowledged that genetics plays a role in determining who develops AD and SD, that of interacting with environmental factors.

Strength of association

The stronger the association, the greater the case for causality. Both fat and total caloric supply have very high associations (r^2 = 0.932 and 0.880, respectively).

Consistency of association

The case for causality is increased if similar results are found among many populations. The results shown in Figures 1 and 2 show that AD prevalence is based primarily on fat and caloric supply, with results from 11 countries on four continents, and span the latitude range from 60°N to 1°N.

Temporal relationship

The cause should precede the effect. Both of the analyses of the interval between the study and the dietary factors indicate that the highest correlations occur for an interval 3-5 years prior to the study.

Dose-response relationship

There should be a linear dose-response relationship for low doses. The regression relationships shown in Figures 1 and 2 are linear.

Biological plausibility

The relationship should be consistent with the known laws of biology, chemistry, and physics. It has been shown that the epidemiological associations with diet are matched by the mechanisms of how the diet affects body chemistry in increasing the oxidative stress on the body and, in turn, how increases in oxidative stress lead to changes in the brain associated with AD.

Coherence of the association with other known facts

Increased oxidative stress has been hypothesized as the cause of AD [Harman, 1995; Smith et al., 1997b], and is associated with a large variety of CDDs [Harman, 1996]. Table 5 shows that the prevalence of AD and many other CDDs is highly correlated throughout the world. Other studies discussed in this paper report that the risk of developing AD can be affected by diet [Kalmijn et al., 1997] and dietary supplements [Sano et al., 1997] related to oxidative stress. The findings that clinical expression of AD is strongly enhanced by strokes [Hulette et al., 1997; Snowdon et al., 1997] and that risk of developing dementia after ischemic strokes is increased [Kokmen et al., 1996b] are consistent with the oxidative-stress hypothesis. Note that dementia and stroke seem to be interrelated, as development of dementia after stroke increases the risk of stroke recurrence [Moroney et al., 1997]. The results of this study are also consistent with the role of fats in causing inflammation and in fish and fish oil in reducing inflammation. There is no basic conflict between the findings about diet in this paper and many other studies of risk factors for AD since they did not investigate the dietary aspects of the populations investigated [e.g., the review in Katzman and Kawas, 1994].

Experimental manipulation

The strength of the case for causality is increased if experiments can be performed in which increasing the dose increases the response and decreasing the dose decreases the response. The vitamin E [Sano et al., 1997], linoleic acid and fish [Kalmijn et al., 1997] consumption studies, and the NSAIDs study [Stewart et al., 1997] are important steps in this direction. Additional such studies are to be encouraged.

Analogy

Other CDDs have been shown to be caused by or associated with high fat or total caloric consumption (see Table 6). Most CDDs seem to have a dietary cause according to the Burden of Disease study [Murray and Lopez, 1996a,b].

Summary on causality

In summary, most of the tests generally applied to determine whether an association is a causal one seem to be satisfied, thereby strongly supporting and quantifying the hypothesis that fat consumption, with assistance from total caloric consumption, is the primary cause of AD. However, while much additional research is required to confirm this conclusion and develop dietary and supplements guidelines for the prevention and treatment of Alzheimer's disease, the information contained herein should be useful in these regards.

Prevention of Alzheimer's disease

There is strong evidence that the incidence and prevalence of AD is affected by diet, with high risk factors found to include alcohol, fat, refined carbohydrates, salt, and total caloric consumption, and preventative factors found to include antioxidants, essential trace minerals, estrogen for post-menopausal women, fish and fish oil, and anti-inflammatory therapeutic agents. In addition, since exercise has been found to reduce the incidence of stroke for men (no corresponding effect was found for women) [Kiely et al., 1994], exercise should also reduce the risk of developing AD. Thus, healthy diets should be considered the first line of defense against both the development and progression of AD, as well as all other chronic degenerative diseases. The finding that the highest correlation between diet and AD incidence and prevalence is found 3-5 years before the study period suggests that diet modifications late in life can still affect the risk of developing AD.

In addition to the analysis on how to combat oxidative stress caused by diet by Harman [1996] there are other popular books on recommended diets to prevent chronic degenerative disease [e.g., Kronhausen and Kronhausen, 1989; Ornish et al., 1990; Robbins, 1992; Ames et al., 1993; Kushi and Jack, 1993; Moore, 1993; Barnard, 1995; Sciullo and Wade, 1995; Carper, 1996; Harman, 1996] and on dietary supplements [Balch and Balch, 1997]. Despite the fact that these references were aimed at different conditions, the recommendations in them have much in common and are generally consistent with the findings of the meta-analysis presented here.

Acknowledgements

The author thanks O. L. Loucks (Dept. of Zoology, Miami University, Oxford, Ohio) for helping him to develop a working knowledge of the meta-analysis of epidemiological studies; L. R. White (Honolulu-Asia Aging Study) and E. Kamhi (Natural Alternatives, Oyster Bay, NY) for helpful discussions; G. D. Considine (Hampton, Va.) for helpful comments on statistics; J. W. Geddes, Editor of Alzheimer's Disease Review and two anonymous referees for useful comments on the manuscript; MedLine Professional for easy access to the current literature; and the Moorman Memorial Library of the Eastern Virginia Medical School (Norfolk, Va.) and the Health Sciences Library of the Riverside School of Professional Nursing (Newport News, Va.) for use of their facilities and extensive journal collections.

References

Ahlgren, J.D. (1996) Epidemiology and risk factors in pancreatic cancer. *Seminars in Oncology* 23, 241-250.

Aisen, P.S. and Davis, K.L. (1997) The search for disease-modifying treatment for Alzheimer's disease. *Neurol* 48 (Suppl 6) S35-S41.

Alzheimer, A. (1907) Über eine eigenartige Erkrankung der Hirnonde? *Allgemeine Zeitschrift für Psychiartie und Psychish-Gerichtlich Medicin* 64, 146-148.

American Psychiatric Assoc. (1980) *Diagnostic and Statistical Manual of Mental Disorders*, 3rd Edit., Washington, DC.

Ames, B.N., Shigenaga, M.K. and Hagen, T.M. (1993) Oxidants, antioxidants, and the degenerative diseases of aging. *Proc Natl Acad Sci USA* 90, 7915-7922.

Bachman, D.L., Wolf, P.A., Linn, R., Knoefel, J.E., Cobb, J., Belanger, A., D'Agostino, R.B. and White, L.R. (1992) Prevalence of dementia and probable senile dementia of the Alzheimer type in the Framingham Study. *Neurol* 42, 115-119.

Balch, J.F. and Balch, P.A. (1997) *Prescription for Nutritional Healing*, Avery Pub. Group, Garden City Park, NY.

Barnard, N. (1995) *Eat Right, Live Longer*, Harmony Books, New York, NY.

Beard, C.M., Kokmen, E., Offord, K.P. and Kurland, L.T. (1992) Lack of association between Alzheimer's disease and education, occupation, marital status, or living arrangement. *Neurol* 42, 2063-2068.

Beard, C.M., Kokmen, E., O'Brien, P.C. and Kurland, L.T. (1994) Are patients with Alzheimer's disease surviving longer in recent years? *Neurol* 44, 1869-1871.

Blacker, D., *et al*. (1997) ApoE-4 and age at onset of Alzheimer's disease. *Neurol* 48, 139-147.

Bolla, K.I., Briefel, G., Spector, D., Schwartz, B.S., Wieler, L., Herron, J. and Gimenez, L. (1992) Neurocognitive effects of aluminum. *Arch Neurol* 49, 1021-1026.

Breitner, J.C.S. and Welsh, K.A. (1995) Genes and recent developments in the epidemiology of Alzheimer's disease and related dementia. *Epidemiol Rev* 17, 39-47.

Breteler, M.M.B., Claus, J.J., van Duijn, C.M., Launer, L.J. and Hofman, D. (1992) Epidemiology of Alzheimer's disease. *Epidemiol Rev* 14, 59-82.

Broe, G.A., Henderson, A.S., Creasey, H., McCusker, E., Korten, A.E., Jorm, A.F., Longley, W. and Anthony, J.C. (1990) A case-control study of Alzheimer's disease in Australia. *Neurol* 40, 1698-1707.

Butterfield, D.A. (1996) Commentary: Alzheimer's disease: A disorder of oxidative stress. *Alzheimer's Dis Rev,* 1, 68-70.

Calvert, R.J., Klurfeld, D.M., Subramaniam, S., Vahouny, G.V. and Kritchevsky, D. (1987) Reduction of colonic carcinogenesis by wheat bran independent of fecal bile acid concentration. *J Natl Cancer Inst* 79, 875-880.

Carper, J. (1993) *Food - Your Miracle Medicine*. HarperCollins, New York, NY.

Carper, J. (1996) *Stop Aging Now!* HarperCollins, New York, NY.

Carroll, K.K. (1987) Experimental studies on dietary fat and cancer in relation to epidemiological data, in Ip, C., Birt, D, Rogers, A.E. and Mettlin, C., eds., *Dietary Fat and Cancer*, A.R. Liss, New York, NY.

Casdorph, H.R. and Walker, M. (1995) *Toxic Metal Syndrome*, Avery Pub. Group, Garden City Park, NY.

Christensen, O. and Christensen, E. (1988) Fat consumption and schizophrenia. *Acta Psychiatr Scand* 78, 587-591.

Clausen, J. (1984) Demential syndromes and the lipid metabolism. *Acta Neurol Scand* 70, 345-355.

Darlington, G. and Gamlin, L. (1996) *Diet and Arthritis*, Vermillion, Ebury Press, Random House, London.

Davis, R.E., *et al.* (1997) Mutations in mitochondrial cytochrome *c* oxidase genes segregate with late-onset Alzheimer disease. *Proc Nat Acad Sci USA* 94, 4464-4569.

Disterhoft, J.F., Gispen, W.H., Traber, J. and Khachaturian, Z.S. (eds.) (1994) *Calcium Hypothesis of Aging and Dementia*. Ann N Y Acad Sci 747.

Doll, R. (1993) Review: Alzheimer's disease and environmental aluminium. *Age Ageing* 22, 138-153.

Ehmann, W.D., Markesbery, W.R., Alauddin, M., Hossain, T.I.M. and Brubaker, E.H. (1986) Brain trace elements in Alzheimer's disease. *NeuroToxicol* 7, 197-206.

Erasmus, U. (1993) *Fats that Heal, Fats that Kill*, Alive Books, Burnaby, BC, Canada.

Evans, D.A., *et al.* (1989) Prevalence of Alzheimer's disease in a community population of older persons. *JAMA* 262, 2551-2556.

Evans, D.A., Beckett, L.A., Field, T.S., Feng, L., Albert, M.S., Bennett, D.A., Tycko, B. and Mayeux, R. (1997) Apolipoprotein E4 and incidence of Alzheimer disease in a community population of older persons. *JAMA* 277, 822-824.

Fahn, S. and Cohen, G. (1992) The oxidant stress hypothesis in Parkinson's disease: Evidence supporting it. *Ann Neurol* 32, 804-812.

Farlow, M., Murrell, J., Ghetti, B., Unverzagt, F., Zeldenrust, S. and Benson, M. (1994) Clinical characteristics in a kindred with early-onset Alzheimer's disease and their linkage to a G—>T change at position 2149 of the amyloid precursor protein gene. *Neurol* 44, 105-111.

Finch, C.E. and Cohen, D.M. (1997) Aging, metabolism, and Alzheimer disease: Review and hypothesis. *Experiment Neurol* 143, 82-102.

Food and Agriculture Organization (FAO) of the United Nations (1991) *Food Balance Sheets*, Rome, Italy.

Forbes, W.F. and McLachlan, D.R.C. (1996) Further thoughts on the aluminum-Alzheimer's disease link. *J Epidemiol Commun Health* 50, 401-403.

Fox, N.C., Warrington, E.K., Freeborough, P.A., Hartikainen, P., Kennedy, A.M., Stevens, J.M. and Rossor, M.N. (1996) Presymptomatic hippocampal atrophy in Alzheimer's disease, A longitudinal MRI study. *Brain* 119, 2001-2007.

Fratiglioni, L., Grut, M., Forsell, Y., Viitanen, M. Frafström, M., Holmén, K. Ericsson, K., Bäckman, L., Ahlbom, A. and Winbland, B. (1991) Prevalence of Alzheimer's disease and other dementias in an elderly urban population: Relationship with age, sex, and education. *Neurol* 41, 1886-1892.

Fukunishi, I., Hayabara, T. and Hosokawa, K. (1991) Epidemiological surveys of senile dementia in Japan. *Int J Soc Psychiatry* 37, 51-56.

Graves, A.B., Larson, E.B., Edland, S.D., Bowen, J.D., McCormick, W.C., McCurry, S.M., Rice, M.M., Wenzlow, A. and Uomoto, J.M. (1996) Prevalence of dementia and its subtypes in the Japanese American population of King County, Washington State. *Am J Epidemiol* 144, 760-771.

Gridley, T. (1996) Notch, stroke and dementia. *Nature* 383, 673.

Harman, D. (1956) Aging: A theory based on free radical and radiation chemistry. *J Geront* 11, 298-300.

Harman, D. (1994) Aging: Prospects for further increases in the functional life span. *Age* 17, 119-146.

Harman, D. (1995) Free radical theory of aging: Alzheimer's disease pathogenesis. *Age* 18, 97-119.

Harman, D. (1996) Aging and disease: extending functional life span. *Ann N Y Acad Sci* 786 321-336.

Harris, W.S. (1997) n-3 Fatty acids and serum lipoproteins: human studies. *Am J Clin Nutr* 65(suppl) 1645S-1654S.

Hasegawa, K., Homma, A. and Imai, Y. (1986) An epidemiological study of age-related dementia in the community. *Int J Geriatr Psychiatry* 1, 45-55.

Hayflick, L. (1996) *How and Why we Age*, Ballantine Books, New York, NY.

Hébert, R. and Brayne, C. (1995) Epidemiology of vascular dementia. *Neuroepidemiol*, 14, 240-257.

Hegsted, D.M. (1986) Calcium and osteoporosis. *J Nutr* 116, 2316-2319.

Hendrie, H.C., Osuntokun, B.O., Hall, K.S., *et al.* (1995) Prevalence of Alzheimer's disease and dementia in two communities: Nigerian Africans and African Americans. *Am J Psychiatry* 152, 1485-1492.

Hensley, K., *et al.* (1996) Reactive oxygen species as causal agents in the neurotoxicity of the Alzheimer's disease-associated amyloid beta peptide. *Ann N Y Acad Sci* 786, 120-134.

Heyman, A., Wilkinson, W.E., Stafford, J.A., Helms, M.J., Sigmon, A.H. and Weinberg, T. (1984) Alzheimer's disease: A study of epidemiological aspects. *Ann Neurol* 15, 335-341.

Heyman, A., Fillenbaum, G., Prosnitz, B., Raiford, K., Burchett, B. and Clark, C. (1991). Estimated prevalence of dementia among elderly black and white community residents. *Arch Neurol* 48, 594-598.

Hill, A.B. (1965) The environment and disease: Association or causality. *Proc R Soc Edinburgh*, 58, 295-300.

Hitchcox, L. (1996) *Long Life Now*, Celestial Arts, Berkeley, Calif.

Hulette, C., Nochlin, D., McKeel, D., Morris, J.C., Mirra, S.S., Sumi, S.M. and Heyman, A. (1997) Clinical-neuropathologic findings in multi-infarct dementia: A report of six autopsied cases. *Neurol* 48, 668-672.

Hunt, M. (1997) *How Science Takes Stock, The Story of Meta-Analysis*, Russell Sage Foundation, New York, NY.

Hursting, S.D., Margolin, B.H. and Switzer, B.R. (1993) Diet and human leukemia: an analysis of international data. *Prevent Med* 22, 409-422.

Jorm, A.F., Korten, A.E. and Henderson, A.S. (1987) The prevalence of dementia: A quantitative integration of the literature. *Acta Psychiatr Scand* 76, 465-479.

Jorm, A.F. (1991) Cross-national comparisons of the occurrence of Alzheimer's and vascular dementias. *Eur Arch Psychiatry Clin Neurosci* 240, 218-222.

Kalmijn, S., Feskens, E.J.M., Launer, L.J. and Kromhout, D. (1997) Polyunsaturated fatty acids, antioxidants, and cognitive function in very old men. *Am J Epidemiol* 145, 33-41.

Katzman, R. and Kawas, C. (1994) The epidemiology of dementia and Alzheimer disease. Ch. 8 in *Alzheimer Disease* (Terry, R.D., Katzman, R. and Bick, K.L., eds.) Raven Press, Ltd., New York, NY, 105-122.

Keefover, R.W. (1996) The clinical epidemiology of Alzheimer's disease. *Neuroepidemiol* 14, 337-351.

Keys, A., (ed.) (1970) *Coronary Heart Disease in Seven Countries*, American Heart Assoc. Monograph Number 29.

Kiely, D.K., Wolf, P.A., Cupples, L.A., et al. (1994) Physical activity and stroke: the Framingham study. *Am J Epidemiol* 140, 608-620.

Kim, D.N., Eastman, A., Baker, J.E., Mastrangelo, A., Sethi, S., Ross, J.Y., Schmeee, J. and Thomas, W.A. (1995) Fish oil, atherogenesis, and thrombogenesis. *Ann N Y Acad Sci* 748, 474-481.

Kokmen, E., Beard, C.M., O'Brien, P.C. and Kurland, L.T. (1996a) Epidemiology of dementia in Rochester, Minnesota. *Mayo Clin Proc* 71, 275-282.

Kokmen, E., Whisnant, J.P., O'Fallon, W.M., Chu, C.-P. and Beard, C.M. (1996b) Dementia after ischemic stroke: A population-based study in Rochester, Minnesota (1960-1984). *Neurol* 19, 154-159.

Kronhausen, E. and Kronhausen, P. (1989) *Formula for Life*, William Morrow & Co., New York, NY.

Kua, E.H. (1991) The prevalence of dementia in elderly Chinese. *Acta Psychiatr Scand* 83, 350-352.

Kushi, M. and Jack, A. (1993) *The Cancer Prevention Diet*. St. Martin's Press, New York, NY.

Lemann, Jr., J., Pleuss, J.A. and Gray, R.W. (1993) Potassium causes calcium retention in healthy adults. *J Nutr* 123, 1623-1626.

Lendon, C.L., Ashall, F. and Goate, A.M. (1997) Exploring the etiology of Alzheimer disease using molecular genetics. *JAMA* 277, 825-831.

Levy-Lahad, E. and Bird, T.D. (1996) Genetic factors in Alzheimer's disease: A review of recent advances. *Ann Neurol* 40, 829-840.

Li, G., Shen, Y.V., Chen, C.H. *et al.* (1989) An epidemiological survey of age-related dementia in an urban area of Beijing. *Acta Psychiatr Scand* 79, 557-563.

Lin, H.N., Tsai, M.T. and Rin, H. (1984) Psychiatric disorders among old people in a rural area: Hung-Ch'un study. *Bull Chin Soc Neurol Psychiatry*, Special Issue 1, 64-79.

Lindsay, J., *et al.* (1994) The Canadian Study of Health and Aging: Risk factors for Alzheimer's disease in Canada. *Neurol* 44, 2073-2080.

Lippa, C.F. *et al.* (1996) Familial and sporadic Alzheimer's disease: Neuropathology cannot exclude a final common pathway. *Am Acad Neurol* 46, 406-412.

Liu, H.-C., Lin, K.-N., Teng, E. L., Wang, S.-J., Fuh, J.-L., Guo, N.-W., Chou, P., Hu, H.-H. and Chiang, B.N. (1995) Prevalence and subtypes of dementia in Taiwan: A community survey of 5297 individuals. *J Am Geriatrics Soc* 43, 144-149.

Lobo, A., Saz, P., Dia, J.L. *et al.* (1990) The epidemiological study of dementia in Zaragoza, Spain, in *Psychiatry: A World Perspective, Proc. of the VIII World Congress of Psychiatry, Athens, Greece, Oct. 13-19, 1989* (Stefaniss, C.N., Soldators, C.R. and Rabavilas, eds.), Elsevier, Amsterdam, The Netherlands, 113-117.

Logroscino, G., Marder, K., Cote, L., Tang, M.-X., Shea, S. and Mayeux, R. (1996) Dietary lipids and antioxidants in Parkinson's disease: A population-based, case-control study. *Ann Neurol* 39, 89-94.

Lutz, J. (1984) Calcium balance and acid-base status of women as affected by increased protein intake and by sodium bicarbonate ingestion. *Am J Clin Nutr* 39, 281-288.

Markesbery, W.R. and Ehmann, W.D. (1994) Brain trace elements in Alzheimer disease. Ch. 22 in *Alzheimer Disease* (Terry, R.D., Katzman, R. and Bick, K.L., eds.) Raven Press, Ltd., NY, 353-367.

Martin, G.M. and Kukull, W.A. (1996) Do cultural differences affect Alzheimer Disease? *JAMA* 276, 993-995.

Martin, R.B. (1994) Aluminum: A neurotoxic product of acid rain. *Accounts of Chemical Res* 27, 204-210.

Massey, L.K. and Whiting, S.J. (1993) Caffeine, urinary calcium, calcium metabolism and bone. *J Nutr* 123, 1611-1614.

Metz, J.A. Anderson, J.B. and Gallagher, Jr., P.N. (1993) Intakes of calcium, phosphorus, and protein, and physical activity level are related to radial bone mass in young adult women. *Am J Clin Nutr* 58, 537-542.

Moore, R. D. (1993) *The High Blood Pressure Solution*, Healing Arts Press, Rochester, Vt.

Moroney, J.T., Bagiella, E., Tatemichi, T.K., Paik, M.C., Stern, Y. and Desmond, D.W. (1997) Dementia after stroke increases the risk of long-term stroke recurrence. *Neurol* 48, 1317-1325.

Morra, M. and Potts, E. (1994) *Choices*. Avon Books, New York, NY.

Morrison-Bogorad, M., Phelps, C. and Buckholtz, N. (1997) Alzheimer disease research comes of age. *JAMA* 277, 837-840.

Mortimer, J.A. and Hutton, J.T. (1985) Epidemiology and etiology of Alzheimer's disease, in *Senile Dementia of the Alzheimer Type* (Hutton, J.T. and Kenny, A.D., eds.) A.R. Liss, Inc., New York, NY, 177-196.

Murray, C.J.L. and Lopez, A.D. (1996a) *Global Health Statistics, Global Burden of Disease and Injury Ser.*, Vol. II, Harvard School of Public Health, Cambridge, Mass.

Murray, C.J.L. and Lopez, A.D. (1996b) Evidence-based health policy—lessons from the Global Burden of Disease Study. *Science* 274, 740-743.

Nordin, B.E.C., Need, A.G., Morris, H.A. and Horowitz, M. (1993) The nature and significance of the relationship between urinary sodium and urinary calcium in women. *J Nutr* 123, 1615-1622.

Norris, J., *et al.* (eds.) (1995) *Professional Guide to Diseases*. 5th edition. Springhouse Corp., Springhouse, Pa.

O'Conner, D.W., Pollitt, P.A., Hyde, J.B., Fellows, J.L., Miller, N.D. and Roth, M. (1990) A follow-up study of dementia diagnosed in the community using the Cambridge Mental Disorders of the Elderly Examination. *Acta Psychiatr Scand* 81, 78-82.

Ornish, D., Brown, S.E., Scherwitaz, L.W., Billings, J.H., Armstrong, W.T., Ports, T.A., McLanahan, S.M., Kirkeeide, R.L., Brand, R.J. and Gould, K.L. (1990) Can lifestyle changes reverse coronary heart disease? *Lancet* 336, 129-133.

Osuntokun, B.O., Hendrie, H.C., Ogunniyi, A.O., Hall, K.S., Lekwauwa, U.G., Brittain, H.M., Norton, Jr., J.A., Oyediran, A.B., Pillay, N. and Rodgers, D.D., (1992) Cross-cultural studies in Alzheimer's disease. *Ethnicity Dis* 2, 352-357.

Pearson, D. and Shaw, S. (1982) *Life Extension, A Practical Scientific Approach*, Warner Books, New York, NY.

Pitchford, P. (1993) *Healing with Whole Foods*. North Atlantic Books, Berkeley, Calif.

Prince, M., Cullen, M. and Mann, A. (1994) Risk factors for Alzheimer's disease and dementia: A case-control study based on the MRC elderly hypertension trial. *Neurol* 44, 97-104.

Quagliano, J.V. and Vallarino, L.M. (1969) *Chemistry*. 3d edition, Prentice-Hall, Englewood Cliffs, NJ.

Reddy, B.S. (1993) Dietary fat, calories, and fiber in colon cancer. *Prevent Med* 22, 738-749.

Reinhold, J.G. (1971) High phytate content of rural Iranian bread: a possible cause of human zinc deficiency. *Am J Clin Nutr* 24, 1204-1205.

Renton, A. (1994) Epidemiology and causation: A realist view. *J Epidemiol Commun Health* 48, 79-85.

Rexrode, K.M., Hennekens, C.H., Willett, W.C., Colditz, G.A., Stampfer, M.J., Rich-Edwards, J.W., Speizer, F.E. and Manson, J.E. (1997) A prospective study of body mass index, weight change, and risk of stroke in women. *JAMA* 227, 1539-1545.

Riggs, J.E. (1996) Changing demographics and neurologic disease in the elderly. *Neurol Clin* 14, 477-486.

Rin, H., Huang, M.G. and Tseng, M.C. (1987) Prevalence of elderly dementias in Taipei area. *Proc Ann Meeting Soc Neurol Psychiatry, ROC,* 24.

Robbins, J. (1992) *May All Be Fed, Diet for a New World.* William Morrow and Co., Inc. New York, NY.

Robinson, D.R. (1997) Regulation of prostaglandin synthesis by antiinflammatory drugs. *J Rheumatol* 24(suppl 47) 32-39.

Rocca, W.A., Amaducci, L.A. and Schoenberg, B.S. (1986) Epidemiology of clinically diagnosed Alzheimer's disease. *Ann Neurol* 19, 415-424.

Rocca, W.A., Bonaiuto, S., Lippi, A., Luciani, P., Turtù, F., Cavarzeran, F. and Amaducci, L. (1990) Prevalence of clinically diagnosed Alzheimer's disease and other dementing disorders: A door-to-door survey in Appignano, Macerata Province, Italy. *Neurol* 40, 626-631.

Rose, D.P., Boyar, A.P. and Wynder, E.L. (1986) International comparisons of mortality rates for cancer of the breast, ovary, prostate, and colon, and per capita food consumption. *Cancer* 58, 2363-2371.

Rouse, I.L., Armstrong, B.K., Beilin, L.J. and Vandongen, R. (1984) Vegetarian diet, blood pressure and cardiovascular risk. *Aust NZ J Med* 14, 439-443.

Salonen, J.T., Salonen, R., Ihanainen, M., Parvianian, M., Seppänen, R., Kantola, M., Seppänen, K. and Rauramaa, R. (1988) Blood pressure, dietary fats, and antioxidants. *Am J Clin Nutr* 48, 1226-1232.

Sano, M., *et al.* (1997). A controlled trial of slegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. *New Eng J Med* 336, 1216-1222.

Savory, J., Exley, C., Forbes, W.F., Huang, Y., Joshi, J.G., Kruck, T., McLachlan, D.R.C. and Wakayama, I. (1996) Can the controversy of the role of aluminum in Alzheimer's disease be resolved? What are the suggested approaches to this controversy and methodological issues to be considered? *J Toxicology and Environ Health* 48, 615-635.

Schoenberg, B.S. (1986) Epidemiology of Alzheimer's disease and other dementing illnesses. *J Chron Dis* 39, 1095-1104.

Sciullo, L.M. and Wade, S.D. (eds.) (1995) *High Blood Pressure Lowered Naturally*, FC&A Publishing Co., Peachtree City, Ga.

Selkoe, D.J. (1997) Alzheimer's disease: Genotypes, phenotype, and treatment. *Science* 275, 630-631.

Shibayama, H., Kasahara, Y. and Kobayashi, H. (1986) Prevalence of dementia in a Japanese elderly population. *Acta Psychiatr Scand* 74, 144-151.

Shinton, R., Sagar, G. and Beevers, G. (1995) Body fat and stroke: Unmasking the hazards of overweight and obesity. *J Epidemiol Commun Health* 49, 259-264.

Siegel, M. (1993) Smoking and leukemia: Evaluation of a causal hypothesis. *Am J Epidemiol* 138, 1-9.

Silman, A.J., Ollier, W., Holligan, S., Birrell, F., Adebajo, A., Asuzu, M. C., Thomson, W. and Pepper, L. (1993) Absence of rheumatoid arthritis in a rural Nigerian population. *J Rheumatol* 20, 618-622.

Smith, M.A. and Perry, G. (1995) Free radical damage, iron, and Alzheimer's disease. *J Neurol Sci* 134 (suppl), 92-94.

Smith, M.A., Sayre, L. and Perry, G. (1996a) Is Alzheimer's a disease of oxidative stress? *Alzheimer's Dis Rev* 1, 63-67.

Smith, M.A., Sayre, L. and Perry, G. (1996b) Diabetes mellitus and Alzheimer's disease: glycation as a biochemical link. *Diabetologia* 39, 247.

Smith, M.A., Sayre, L. and Perry, G. (1997a) Morphological aspects of oxidative damage in Alzheimer's disease in Beal, M.F., Howell, H, and Bodis-Wollner, I. (eds.) *Mitochrondria and Free Radicals in Neurodegenerative Diseases*, Wiley-Liss, Inc., New York, NY.

Smith, M.A., Sayre, L. and Perry, G. (1997b) Oxidative damage in Alzheimer disease, *Neurogerontology and Neurogeriatrics*, in press.

Snowdon, D.A., Greiner, L.H., Mortimer, J.A., Riley, K.P., Greiner, P.A. and Markesbery, W.R. (1997) Brain infarction and the clinical expression of Alzheimer's disease, The Nun Study. *JAMA* 277, 811-817.

Stadtman, E.R. (1992) Protein oxidation and aging. *Science* 259, 381-384.

Stern, Y., *et al.* (1997) Predicting time to nursing home care and death in individuals with Alzheimer disease. *JAMA* 277, 806-812.

Stewart, W.F., Kawas, C., Corrada, M. and Metter, E.J. (1997) Risk of Alzheimer's disease and duration of NSAID use. *Neurol* 48, 626-632.

Sulkava, R., Wikström, J., Aromaa, A., Ratiasalo, R., Lehtinen, V., Lahtela, K. and Palo, J. (1985) Prevalence of severe dementia in Finland. *Neurol* 35, 1025-1029.

Surgeon General's Report on Nutrition and Health, (1988) U.S. Dept. of Health and Human Services, Wash., DC.

Tang, M.-X., *et al.* (1996a) Relative risk of Alzheimer disease and age-at-onset distributions, based on APOE genotypes among elderly African Americans, Caucasians, and Hispanics in New York City. *Am J Hum Genet* 58, 574-584.

Tang, M.-X., Jacobs, D., Stern, Y., Marder, K., Schofield, P., Gurland, B., Andrews, H. and Mayeux, R. (1996b) Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. *Lancet* 348, 429-432.

Thompson, C.M., Markesbery, W.R., Ehmann, W.D., Mao, Y.-X. and Vance, D.E. (1988) Regional brain trace-element studies in Alzheimer's disease. *NeuroToxicol* 9, 1-8.

Tillotson, J.L., Kato, H., Nichaman, M.Z., Miller, C., Gay, M.L., Johnson, K.G. and Rhoads, G.G. (1973) Epidemiology of coronary heart disease and stroke in Japanese men living in Japan, Hawaii, and California: Methodology for comparison of diet. *Am J Clin Nutr* 26, 177-184.

Ueda, K., Kawano, H., Hasuo, Y. and Fujishima, M. (1992) Prevalence and etiology of dementia in a Japanese community. *Stroke* 23, 798-803.

U.S. Bureau of the Census (1996) *Current Population Reports, Special Studies, P23-190, 65+ in the United States*, U.S. Gov Print Off, Washington, DC.

U.S. Dept. of Commerce (1975) *Historical Statistics of the United States, Colonial Times to 1970*, Ser. B 447, p. 85.

U.S. Dept. of Commerce (1994) *Statistical Abstract of the United States 1994*, Table 219.

van Duijn, C.M. (1996) Epidemiology of the dementias: recent developments and new approaches. *J Neurol, Neurosurg, and Psychiatry* 60, 478-488.

Wade, C. (1992) *Eat Away Illness*. Parker Pub. Co., West Nyack, NY.

Walford, R.L. (1986) *The 120 Year Diet*, Pocket Books, New York, NY.

Walford, R.L. and Walford, L. (1994) *The Anti-Aging Plan*, Four Walls Eight Windows, New York, NY.

Weberg, R. and Berstad, A. (1986) Gastrointestinal absorption of aluminium from single doses of aluminium containing antacids in man. *Europ J Clin Investig* 16, 428-432.

Weisburger, J.H. (1990) Causes of cancer and cancer prevention. *Arch Geschwulfstforsch* 60, 385-399.

Weisburger, J.H. (1996) Tea antioxidants and health. Ch. 15 in *Handbook of Antioxidants*, Cadenas, E. and Packer, L. (eds). Marcel Dekker, Inc. New York, NY.

Weisburger, J.H. and Williams, G.M. (1995) Causes of cancer, Ch. 2 in Murphy, G.P., Lawrence, Jr., W. and Lenhard, Jr., R.E. (eds.) *American Cancer Soc. Textbook of Clinical Oncology*, 2nd Edit., Am. Cancer Soc., Atlanta, Ga., 10-39.

Wenstrup, D., Ehmann, W.D. and Markesbery, W.R. (1990) Trace element imbalances in isolated subcellular fractions of Alzheimer's disease brains. *Brain Res* 533, 125-131,

White, L.R. (1992) Towards a program of cross-cultural research on the epidemiology of Alzheimer's disease. *Current Sci* 63, 456-469.

White, L., *et al.* (1996) Prevalence of dementia in older Japanese-American men in Hawaii. *J Am Med Assoc* 276, 955-960.

Wills, M.R. (1973) Intestinal absorption of calcium. *Lancet* 1, 820-821.

Wright, J.W., ed. (1995) *The Universal Almanac, 1996*, Andrews and McMeel, Kansas City, Mo., p. 370.

Wydner, E.L., Rose, D.P. and Cohen, L.A. (1986) Diet and breast cancer in causation and therapy. *Cancer* 58, 1804-1813.

Yan, S.D., Schmidt, A.M., Anderson, G.M., Zhang, J., Brett, J., Zou, Y.S., Pinsky, D. and Stern, D. (1994) Enhanced cellular oxidant stress by the interaction of advanced glycation end products with their receptors/binding proteins. *J Biol Chem* 269, 9889-9897.

Yan, S.D., *et al.* (1997) Amyloid-ß peptide-receptor for advanced glycation endproduct interaction elicits neuronal expression of macrophage-cology stimulating factor: A proinflammatory pathway in Alzheimer disease. Proc Natl Acad Sci USA 94, 5296-5301.

Yu, B.P. (1994) How diet influences the aging process of the rat. *Proc Soc Experiment Biol Med* 205, 97-105.

Zhang, M., Katzman, R., Salmon, D., *et al.* (1990) The prevalence of dementia and Alzheimer's diseases in Shanghai, China: Impact of age, gender, and education. *Ann Neurol* 27, 428-437.

Zhao, L.P., *et al.* (1991) Effects of saturated fat on lung, prostate, and breast cancer in five ethnic groups of Hawaii. Abstract. *Am J Clin Nutr* 53, P-31.