HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol. Clin. Exp. **15**, 1–70 (2000)

A Unifying Hypothesis of Alzheimer's Disease. III. Risk Factors

KURT HEININGER*
Department of Neurology, Heinrich Heine University, Dusseldorf, Germany

Normal ageing and Alzheimer's disease (AD) have many features in common and, in many respects, both conditions only differ by quantitative criteria. A variety of genetic, medical and environmental factors modulate the ageing-related processes leading the brain into the devastation of AD. In accordance with the concept that AD is a metabolic disease, these risk factors deteriorate the homeostasis of the Ca^{2+}–energy–redox triangle and disrupt the cerebral reserve capacity under metabolic stress. The major genetic risk factors (APP and presenilin mutations, Down's syndrome, apolipoprotein E4) are associated with a compromise of the homeostatic triangle. The pathophysiological processes leading to this vulnerability remain elusive at present, while mitochondrial mutations can be plausibly integrated into the metabolic scenario. The metabolic leitmotif is particularly evident with medical risk factors which are associated with an impaired cerebral perfusion, such as cerebrovascular diseases including stroke, cardiovascular diseases, hypo- and hypertension. Traumatic brain injury represents another example due to the persistent metabolic stress following the acute event. Thyroid diseases have detrimental sequela for cerebral metabolism as well. Furthermore, major depression and presumably chronic stress endanger susceptible brain areas mediated by a host of hormonal imbalances, particularly the HPA-axis dysregulation. Sociocultural and lifestyle factors like education, physical activity, diet and smoking may also modulate the individual risk affecting both reserve capacity and vulnerability. The pathophysiological relevance of trace metals, including aluminum and iron, is highly controversial; at any rate, they may adversely affect cellular defences, antioxidant competence in particular. The relative contribution of these factors, however, is as individual as the pattern of the factors. In familial AD, the genetic factors clearly drive the sequence of events. A strong interaction of fat metabolism and apoE polymorphism is suggested by intercultural epidemiological findings. In cultures, less plagued by the 'blessings' of the 'cafeteria diet–sedentary' Western lifestyle, apoE4 appears to be not a risk factor for AD. This intriguing evidence suggests that, analogous to cardiovascular diseases, apoE4 requires a hyperlipidaemic lifestyle to manifest as AD risk factor. Overall, the etiology of AD is a key paradigm for a gene-environment interaction. Copyright © 2000 John Wiley & Sons, Ltd.

KEY WORDS — Alzheimer's disease; risk factors; Down's syndrome; APP; presenilin; apolipoprotein E; traumatic brain injury; cerebrovascular disease; cardiovascular disease; hypertension; major depression; stress; education; diet; smoking; physical activity; trace metals

THE RISK FACTORS

Various genetic and environmental risk factors have been identified. Case-controlled and community-based studies suggest that a variety of factors contribute to the clinical manifestation of AD, particularly late-onset AD. In the aetiology of AD a paradigmatic gene-environment interaction is manifested.

GENETICS

Many epidemiological studies have shown that a positive family history is a consistent risk factor for AD (Heyman *et al.*, 1984; Mendez *et al.*, 1992). This led to the early notion that AD has a genetic underpinning. So far, mutations in three genes have been identified as causally related to familial early-onset AD (EOAD). These three genes explain most of the highly penetrant EOAD. However, overall these gene mutations represent less than 10 per cent of all AD cases.

Mutations of the amyloid precursor protein gene on chromosome 21

The interest of geneticists in the chromosome 21 (C21) was fuelled by two factors: (i) subjects with Down's syndrome are trisomic for all or part of

*Correspondence to: Kurt Heininger, Hildener Str. 77, 40597 Dusseldorf, Germany.

CCC 0885–6222/2000/010001–70$17.50

C21, and, aged over 35 years, regularly develop AD-like neuropathology, (ii) APP, the mother protein of Aβ, is encoded by a gene which maps to C21 (Robakis *et al*., 1987; St George-Hyslop *et al*., 1987; Tanzi *et al*., 1987). As result of a meticulous search, allelic heterogeneous mutations in the APP gene just distal to the C-terminus and at the N-terminus of the Aβ domain that cosegregate with the AD phenotype have been identified (Chartier-Harlin *et al*., 1991; Goate *et al*., 1991; Murrell *et al*., 1991). Though mutations in the gene for APP account for only a small fraction of cases of early-onset FAD, totalling some 20 families worldwide (Hardy, 1997), the heuristic value of these findings was eminent, indicating that Aβ is involved in the etiology of AD.

Pathophysiologically, the mutant APP familial diseases exhibit the AD-typic pattern of an impaired Ca^{2+}–energy–redox triangle. Carriers of APP mutations have a parietotemporal glucose hypometabolism even in asymptomatic individuals (Kennedy *et al*., 1955). Abnormalities of glucose metabolism (Sorbi *et al*., 1995) and Ca^{2+} homeostasis (Tatebayashi *et al*., 1995; Gibson *et al*., 1997) are also found in non-neuronal cells. Intriguingly, some APP mutations alter the signalling-function of APP with regard to G_o activation (Okamoto *et al*., 1996) (a regulator of Ca^{2+} channels) which may mediate their pro-apoptotic actions (Yamatsuji *et al*., 1996; Giambarella *et al*., 1997). α-ketoglutarate dehydrogenase activity in brains and fibroblasts is reduced similar to sporadic cases (Gibson *et al*., 1998), corroborating that the pathophysiological processes of familial and sporadic cases share common pathways. APP mutations found in familial AD caused an impaired neuronal plasticity with defective neurite extension and synaptic transmission and thus may already give rise to deficits during brain development (Li *et al*., 1997; Hsia *et al*., 1999).

The histopathological changes in EOAD are the ones typical for AD brains, including the cytoskeletal pathology (Ghetti *et al*., 1992; Lantos *et al*., 1992; Nochlin *et al*., 1993). The mutations result in alternative processing of APP (Haass *et al*., 1994) in both the secretory and endocytic pathways (Felsenstein *et al*., 1994; Matsumoto, 1994; Perez *et al*., 1996) and increase Aβ production of neurons (Citron *et al*., 1992, Cai *et al*., 1993) and peripheral cells (Citron *et al*., 1994). The Aβ42 variant is preferentially produced by mutant APP-transfected cells (Suzuki *et al*., 1994; Maruyama *et al*., 1996), deposited in the brains (Kalaria *et al*., 1996; Tamaoka *et al*., 1998) and increased in familial AD plasma (Kosaka *et al*., 1997).

Transgenic mice expressing mutant APP mimic some of the prominent behavioural and pathological features of AD (reviewed by Hsiao, 1998; Price *et al*., 1998). This model disease leads to cognitive impairment (Hsiao *et al*., 1996; Moechars *et al*., 1999), abnormal synaptic transmission and impaired long-term potentiation (Chapman *et al*., 1999; Moechars *et al*., 1999), increased brain levels of Aβ, particularly Aβ42, and decreased levels of sAPP (Hsiao *et al*., 1996; Johnson-Wood *et al*., 1997; Moechars *et al*., 1999), mitochondrial dysfunction (Talpade *et al*., 1998), and increased oxidative stress (Pappolla *et al*., 1998). Cerebrovascular dysregulation is associated with an increased susceptibility to ischemic brain damage (Zhang *et al*., 1997). Alzheimer's disease-like pathology (Games *et al*., 1995; Sturchler-Pierrat *et al*., 1997) includes Aβ deposition (Hsiao *et al*., 1996; Johnson-Wood *et al*., 1997), neuron loss (LaFerla *et al*., 1996; Calhoun *et al*., 1998), necrosis and apoptosis (LaFerla *et al*., 1996; Masliah *et al*., 1996a; Moechars *et al*., 1996), gliosis and neuritic dystrophy (LaFerla *et al*., 1996; Masliah *et al*., 1996a; Moechars *et al*., 1996), microglial activation and clustering within plaques (Games *et al*., 1995; Frautschy *et al*., 1998). Expression of mutant APP in cultured cells causes G protein-mediated apoptosis (Giambarella *et al*., 1997).

Mutations of presenilin 1 on chromosome 14 and presenilin 2 on chromosome 1

Chromosomes 14 and 1 harbour loci of genetic mutations, which in an almost fully penetrant fashion cause familial AD with age of onset frequently in the 40s (Hardy, 1997; Mattson *et al*., 1998). The genes encode transmembrane proteins which were called presenilins (PS) (Levy-Lahad *et al*., 1995; Rogaev *et al*., 1995; Sherrington *et al*., 1995). PS mutations account for approximately half of the early-onset familial AD cases (Campion *et al*., 1995; Gomez-Isla *et al*., 1997; Cruts *et al*., 1998). So far a multitude of mutations, with one exception, missense mutations, were identified (Cruts and Van Broeckhoven, 1998). However, one of the mutations which was thought to be causally related to AD was later identified as a non-pathogenic polymorphism (Mattila *et al*., 1998). The ApoE allele does not appear to modify the age of onset (Lendon *et al*., 1997).

Though our knowledge about the physiological

role of PS is still fragmentary, a rough pattern is gradually emerging, (Mattson *et al*., 1998). Widely expressed in the nervous system, PS have a role in neuronal differentiation (Capell *et al*., 1977; Hartmann *et al*., 1997; Shen *et al*., 1997; Tokuhiro *et al*., 1998), synaptic plasticity (Parent *et al*., 1999), cell survival (Shen *et al*., 1997) and apoptosis (Deng *et al*., 1996; Wolozin *et al*., 1996; Kim T-W *et al*., 1997). PS-1 and -2 are located in the endoplasmic reticulum (ER), Golgi complex and in vesicular structures of the somatodendritic compartment of neurons, predominantly AD-vulnerable regions (Cook *et al*., 1996; Kovacs *et al*., 1996; Page *et al*., 1996; Capell *et al*., 1997; Culvenor *et al*., 1997) and are expressed in a coordinated fashion (Thinakaran *et al*., 1997). In addition to cooperational roles of the PS, opposing roles cannot be ruled out (Mattson *et al*., 1998). PS are processed endoproteolytically into two fragments (Mercken *et al*., 1996; Thinakaran *et al*., 1996). The cleavage is developmentally regulated (Capell *et al*., 1997; Hartmann *et al*., 1997), but is not necessarily altered by a PS-1 mutation (Mercken *et al*., 1996; Okochi *et al*., 1997). As a 7 transmembrane-spanning receptor-like protein (Dewji and Singer, 1997), PS modulate neuronal excitability, Ca^{2+} homeostasis and transduction signalling (see below), are upregulated by a variety of metabolic stressors such as ischemia, injury, AD, and trisomy 21 (Cribbs *et al*., 1996; Ikeda *et al*., 1998; Tanimukai *et al*., 1998) and appear to protect against these (Giannakopoulos *et al*., 1997). For instance, PS-1 expression, although decreased in the AD hippocampus (Takami *et al*., 1997), is increased in the fraction of NFT-free but decreased in NFT-containing neurons (Giannakopoulos *et al*., 1997). Downregulation of PS-1 expression results in reduced growth and increases susceptibility to apoptosis (Roperch *et al*., 1998). Moreover, PS directly interact with APP, presumably in the ER and Golgi (Waragai *et al*., 1997; Weidemann *et al*., 1997; Xia *et al*., 1997), increase the secretion of sAPP (Marambaud *et al*., 1998) and are required for proper γ-secretase processing of APP (Xia *et al*., 1998). Thus, PS1 deficiency decreases the turnover of the membrane-associated APP and causes carboxyl-terminal fragments of APP to accumulate (De Strooper *et al*., 1998; Xia *et al*., 1998). Another interaction involves intercellular binding of membrane-bound APP and PS, which results in cell–cell adhesion and subsequent, intracellular signalling through tyrosine phosphorylation cascades (Dewji and Singer, 1998).

Presence of the mutant PS-1 gene is associated with reduced perfusion and glucose metabolism of the temporoparietal and cingulate region in affected individuals before and after the development of clinical symptoms (Kennedy *et al*., 1995; Johnson *et al*., 1998). Brains of mutant PS-1 carriers exhibit a massively increased Aβ load and even severe cerebellar pathology (Lemere *et al*., 1996; Mann *et al*., 1996; Tamaoka *et al*., 1998). Plasma levels of Aβ also were found to be increased (Scheuner *et al*., 1996). Compatible with a role of PS in differentiation and neuronal plasticity, in transgenic mice mutant PS-1 impairs the neuronal ability to differentiate (Furukawa *et al*., 1998; Tokuhiro *et al*., 1998), reduces neurite outgrowth (Furukawa *et al*., 1998; Dowjat *et al*., 1999) and alters long-term synaptic plasticity in CA1 hippocampus (Parent *et al*., 1999).

Mutant PS-1 and PS-2 cause a significant increase of APP expression in fibroblasts (Querfurth *et al*., 1995), decrease sAPP production and secretion (Ancolio *et al*., 1997; Marambaud *et al*., 1998), increase total Aβ and Aβ42 intracellular accumulation and secretion in transfected cells and transgenic mice (Borchelt *et al*., 1996; Duff *et al*., 1996; Citron *et al*., 1997; Xia *et al*., 1998) in an age-dependent manner (Duff *et al*., 1996; Oyama *et al*., 1998). Expression of the full-length mutant is required for this capacity, indicating the cooperative interaction of the PS fragments (Tomita *et al*., 1998). Mutant PS also decreased basal ChAT activity in cultured neuronal cells (Pedersen *et al*., 1997).

PS have a role in the regulation of apoptosis which may be modulated by their proteolytic cleavage (Kim T-W *et al*., 1997; Vito *et al*., 1997). Generation of PS-1 and -2 C-terminal fragments delays apoptosis (Vito *et al*., 1997; Vezina *et al*., 1998). PS-1 and -2 mutations, on the other hand, increase cellular vulnerability to apoptosis (Deng *et al*., 1996; Wolozin *et al*., 1996; Guo *et al*., 1998).

Abnormalities of Ca^{2+} regulation, ion channels, signal transduction pathways, oxidative metabolism and antioxidant status were documented in fibroblasts and lymphoblasts of AD patients carrying mutant PS genes (Ito *et al*., 1994; Gibson *et al*., 1996; Latorraca *et al*., 1998). The role of PS in neuronal Ca^{2+} homeostasis may be mediated by intrinsic Ca^{2+} channel properties suggested by homologies to Ca^{2+} channel domains (Sherrington *et al*., 1995), by binding and regulating the activity of a G_o protein (Smine *et al*., 1998), thus modulating Ca^{2+} currents (Hille, 1994), and by upregulating K^+ channel currents (Malin *et al*., 1998). PS-1 over-

expression potentiates Ca^{2+} responses (Paul *et al*., 1997). A missense PS-1 mutation impairs this activity with putative profound sequelae for neuronal excitability (Malin *et al*., 1998). Presenilin-1 mutations alter Ca^{2-} signalling, perturb Ca^{2+} homeostasis and mitochondrial function, enhance oxyradical production in cultured cell lines and synaptosomes and sensitize neurons to apoptosis (Furukawa *et al*., 1998; Guo *et al*., 1998; Begley *et al*., 1999). Both Ca^{2+} influx and release from ER are involved in the pro-apoptotic action of mutant PS-1 (Guo *et al*., 1998). The mutant PS-induced events highlight the importance of the ER Ca^{2+} homeostasis (Meldolesi and Pozzan, 1998) for the cellular vulnerability in conditions of energetic stress (Mattson *et al*., 1998). This role is corroborated by findings that expression of ER stress proteins, including calreticulin which inhibits the intracellular Ca^{2+} rise, protect from oxidative stress (Liu H. *et al*., 1998), that depletion of the ER Ca^{2+} store prevents neuronal injury and death (Waters *et al*., 1997) and that inhibition of ER Ca^{2+}-ATPase can induce apoptosis (Kaneko and Tsukamoto, 1994). The reciprocal association of ER cytochrome c reductase activity, with cholinergic dysfunction and positive correlation with neurofibrillary tangles pathology in AD (Zubenko *et al*., 1990), points at interrelationships of distinct pathophysiologic events. Furthermore, the pathophysiologic relevance of the compromise of ER Ca^{2+} homeostasis in ageing is emphasized (Heininger, 1999a). It is speculated that PS, via their K^+ channel and G_o protein regulating properties, fulfil important functions in Ca^{2+} homeostasis and signalling and by disrupture of these physiologic functions in mutant PS vital neuronal metabolic processes are impaired, resulting in abnormal neuronal plasticity and susceptibility to neurodegeneration.

Down's Syndrome

Down's Syndrome (DS), the most frequent of congenital birth defects, is the consequence of triplication of chromosome 21 (Lejeune *et al*., 1959). The genetic defect results in developmental anomalies, mental retardation and accelerated ageing, the developmental arrest characterized by reduced brain weight and deficient neuro- and synaptogenesis (Wisniewski *et al*., 1984; de la Monte and Hedley-Whyte, 1990).

DS is the most common genetic cause of AD. DS is associated with a high incidence of AD with similar prevalence rates to those in normals, but occurring 30–40 years earlier (Lai and Williams, 1989; Visser *et al*., 1997; Holland *et al*., 1998). Intellectual deterioration is present in approximately one third of patients at the age of 35 and in 50 per cent in the fifth decade of life with fully-fledged dementia (Fenner *et al*., 1987; Brugge *et al*., 1994; Devenny *et al*., 1996; Oliver *et al*., 1998) paralleled by a slowing of the electroencephalogram (Soininen *et al*., 1993). In contrast, the typical neuropathological features of AD, SP and NFT are regularly present in the brains of individuals with DS aged over 35 years (reviewed by Mann, 1993). Thus, in comparison to AD patients, significant differences exist in the correlation of SP density and neuronal loss, atrophy and dementia (Wisniewski and Rabe, 1986; Mann *et al*., 1987; Oliver *et al*., 1998). AD pathology may precede, while dementia and brain atrophy follow and correlate closely (Schapiro *et al*., 1989; Pearlson *et al*., 1990). This phenomenon will be further discussed in part 4 of this series. Similar to AD, middle-aged DS individuals with apoE4 have more impaired and more rapidly declining intellectual functions (Alexander *et al*., 1997b; Del Bo *et al*., 1997) and an increased risk of developing AD earlier, while apoE2 seems to protect DS individuals from AD (Prasher *et al*., 1997; Schupf *et al*., 1998; Tyrrell *et al*., 1998). DS individuals exhibit a range of disordered processes of brain metabolism and homeostasis, which put the neurons under metabolic stress during the whole lifespan. While younger DS individuals show either normal or increased values for regional cerebral glucose utilization (Schwartz *et al*., 1983; Schapiro *et al*., 1990) and blood flow (Risberg, 1980), an AD-like pattern of reduced cerebral glucose metabolism and blood flow can be detected in DS subjects with AD and often in elderly DS individuals without dementia (Melamed *et al*., 1987; Schapiro *et al*., 1988; Azari *et al*., 1994). Typically, older DS subjects show low glucose metabolism during brain stimulation prior to the evolution of dementia (Pietrini *et al*., 1997). Elderly DS individuals display reduced neuronal counts in cortex, hippocampus, basal forebrain, locus coeruleus, raphe and ventral tegmentum (reviewed by Mann, 1993). Similarly, changes of neurotransmitter markers for cholinergic, noradrenergic, serotonergic, glutamatergic and GABAergic neurons are equivalent to the changes seen in AD (reviewed by Mann, 1993). These can be detected already in middle-aged DS individuals (Casanova *et al*., 1985; Godridge *et al*., 1987; Reynolds and Warner, 1988), including a degeneration of basal forebrain neurons (Casanova

et al., 1985). In fifth decade DS subjects, degradation and/or rapid synthesis of brain cell membranes may occur prior to neuronal loss and degeneration (Murata *et al*., 1993). Deficiencies of mitochondrial enzymatic activities were demonstrated in DS platelets (Prince J. *et al*., 1994). DS individuals show increased systemic levels of biomarkers of oxidative stress (Jovanovic *et al*., 1988) and neurons display *in vitro* increased oxygen species and apoptosis (Busciglio and Yankner, 1995). Glycation end products indicating oxidative stress could be detected already in foetal DS brains (Odetti *et al*., 1998). The cerebral metabolic stress may be aggravated by a hypothyroid state. Notably, increased TSH levels indicating a cerebral thyroid hormone shortage predict a poorer cognitive performance (Bhaumik *et al*., 1991), while autoimmune thyroiditis is a common finding in DS subjects and appears to be more pronounced in individuals affected by AD (Percy *et al*., 1990).

As a consequence of the extra C21, expression of APP is increased in ageing Down's Syndrome brains (Rumble *et al*., 1989; Oyama *et al*., 1994; Arai *et al*., 1997), cortical cultures (Yankner *et al*., 1998), lymphocytes and fibroblasts (Govoni *et al*., 1996; Pallister *et al*., 1997) and serum (Rumble *et al*., 1989). In contrast to controls, plasma levels of Aβ are increased (Tokuda *et al*., 1997), soluble Aβ is present in DS brains during the whole lifespan (Teller *et al*., 1996) and, hence, Aβ deposition could be detected in parahippocampal structures as early as in 8 year-old DS patients (Leverenz and Raskind, 1998). Aβ42 deposition precedes and is more abundant, while Aβ40 is only detectable when first signs of neurodegeneration emerge (Iwatsubo *et al*., 1995; Kalaria *et al*., 1996). This gene dosage effect is also present in transgenic mice where the level of neuronal expression of human APP determined the neuroprotective/neurotoxic equilibrium, particularly, in the context of secondary neural injuries (Mucke *et al*., 1996). *In vitro*, overexpression of APP has been demonstrated to induce neuronal degeneration and intracellular accumulation of APP derivatives (Yoshikawa *et al*., 1992). In DS cortical cultures, levels of secreted sAPP and Aβ were reduced, while intracellular Aβ accumulated *in vitro* and *in vivo* (Yankner *et al*., 1998). Overexpression of S-100β that localizes to C21 may also contribute to the accelerated brain ageing and impaired neuronal plasticity (Jørgensen *et al*., 1990; Whitaker-Azmitia *et al*., 1997). A decreased neuronal connectivity and synaptogenesis, which manifests as functional disruption of neural circuits, may already be apparent in children and progress in non-demented DS subjects in their thirties (Ferrer and Gullotta, 1990), Takashima *et al*., 1994). Finally, a precocious immunosenescent status of DS patients may condition the cerebral milieu for the AD-like acute phase response (Griffin *et al*., 1989; Mehta *et al*., 1993; Oka and Takashima, 1997).

Trisomy 16 (TS16) is the mouse correlate of human DS. A partial TS16 mouse (the full TS16 mouse is not viable) shows developmental delay, abnormal behaviour compatible with mental retardation, septohippocampal cholinergic degeneration and astrogliosis (Holtzman *et al*., 1996). TS16 cell lines demonstrate aberrant APP processing and cytoskeleton abnormalities (Williams *et al*., 1998) and show decreased glutathione levels and increased vulnerability (Bambrick *et al*., 1995; Stabel-Burrow *et al*., 1997). Intriguingly, TS16 astroglia elicited a cholinergic deficit when co-cultured with normal neurons from euploid littermates (Nelson *et al*., 1997).

Mutations of mitochondrial DNA

Epidemiological studies suggest an increased risk of late-onset AD in offspring of mothers with AD compared to those of fathers with AD (Heyman *et al*., 1983; Farrer *et al*., 1991; Duara *et al*., 1993; Edland *et al*., 1996), a finding consistent with maternal transmission patterns in AD. Moreover, advanced maternal age at birth may constitute an independent risk in the offspring (Cohen *et al*., 1982; Rocca *et al*., 1991). Mutations in mtDNA were suspected to be causally related since mtDNA is maternally inherited in a non-Mendelian way (Giles *et al*., 1980). Since mtDNA partly encodes four out of five complexes in the oxidative phosphorylation pathway, mutations in mtDNA may result in defective energy homeostasis (Mattson, 1997). A mutation identified as increased in AD patients affects a mitochondrial tRNA gene (Schoffner *et al*., 1993; Hutchin and Cortopassi, 1995; Egensperger *et al*., 1997). This is not a highly penetrant mutation (Tysoe *et al*., 1996) and therefore may have been missed by another group (Wragg *et al*., 1995). Possible consequences for mitochondrial protein synthesis, particularly for complex I (NADH dehydrogenase), have been suggested (Hutchin and Cortopassi, 1995). An increased sensitivity of cells bearing a variety of mtDNA mutations to Ca^{2+}-dependent oxidant stress was shown (Wong and Cortopassi, 1997). Another

report recently demonstrated an increased frequency of a mtDNA 5 kb deletion in AD temporal cortex (Hamblet and Castora, 1997). This type of deletion has been shown previously to be associated with Kearns–Sayre syndrome, a mitochondrial disorder which affects different organ systems. However, as with other mtDNA changes the inherited versus acquired nature remains elusive. mtDNA is exposed to high levels of ROS, but has poor repair mechanism, so that during ageing mtDNA point and length mutations accumulate. The increased oxidative stress associated with AD (Heininger, 1999b) may result in a higher frequency of mutations. A recently reported link between heritable mutations in mtDNA encoding cytochrome oxidases and late-onset AD (Davis *et al*., 1997) could not be confirmed by others (Hutchin *et al*., 1997) and appears to be an artifact (Hirano *et al*., 1997; Wallace *et al*., 1997). Mitochondrial function may also be affected by mutations of nuclear DNA coding for mitochondrial proteins. A polymorphism of the nuclear gene (on chromosome 14) coding for dihydrolipoyl succinyltransferase (DLST), a core component of the α-ketoglutarate dehydrogenase complex, may be an independent risk factor for late onset AD (Nakano *et al*., 1997; Sheu *et al*., 1999a) and appears to be additive to apoE4 (Sheu *et al*., 1999a). It has been claimed that up to 50 per cent of chromosome 14-related early-onset familial AD cases may be due to the DLST polymorphism (Sheu and Blass, 1999). Another DLST genotype, on the other hand, may protect against AD (Sheu *et al*., 1999b). An intriguing finding associated mothers who gave birth to a DS child at a relatively young age (<35 years) with an increased risk for AD (Schupf *et al*., 1994). Another link was suggested for the birth of a DS child and earlier onset of AD in the mother (Heston *et al*., 1981). Causal relationships may be due to a shared susceptibility for an accelerated ageing process (Emanuel *et al*., 1972; Brook *et al*., 1984; Tarin *et al*., 1998) or a maternal balanced chromosome rearrangement which predisposes to the trisomy syndrome, but does not give rise to an unfavourable phenotypic effect.

Apolipoprotein E

Apolipoprotein (apo) E, a 34 kDa molecular weight protein, is the product of a single gene on chromosome 19. It exists in three different alleles, ε2, ε3, ε4, coding for proteins apoE2, apoE3, apoE4, respectively, differing from each other by one or two amino acids, only. Apo E plays a critical role in lipid metabolism through its systemic function in chylomicron and very low density lipoprotein (VLDL) transport. In the individual organs, it acts by redistributing lipids between areas of excess and demand for proliferation and repair. In the brain, apoE is synthesized and secreted primarily by astrocytes and microglia (Pitas *et al*., 1987; Nakai *et al*., 1996; Stone *et al*., 1997) and upregulated following neuronal injury and reinnervation (Poirier *et al*., 1993a). Within the damaged area, apoE scavenges cholesterol and phospholipids from cellular debris and recycles it for membrane remodelling associated with neurite sprouting and synaptic replacement (Poirier *et al*., 1993a). ApoE appears to be necessary for astrocytic lipoprotein secretion (Fagan *et al*., 1998). Moreover, apoE is involved in synaptic integrity, stabilizes the neuronal cytoskeleton, regulates interactions between neurons and extracellular matrix and modulates intracellular Ca^{2+} levels (Masliah *et al*., 1996b; Holtzman and Fagan, 1998). The crucial importance of these mechanisms for neuronal development and networking was highlighted by the findings that apoE-deficient mice display severe learning deficits (Oitzl *et al*., 1997a), and age-dependent reduction of synapses, a complete disruption of the dendritic cytoskeleton (Masliah *et al*., 1995), and a disturbed transbilayer distribution of cholesterol and lipid structure of synaptic membranes (Igbavboa *et al*., 1997). The associated compromised synaptic plasticity (Krugers *et al*., 1997; Holtzman and Fagan, 1998) can be ameliorated by apoE infusions (Masliah *et al*., 1996c) and, in a slice culture, by cholesterol (Teter *et al*., 1998). In transgenic mice produced by transfer of either apoE3 or apoE4 genes to an apoE knockout background, apoE3 and, to a lower extent apoE4, could ameliorate these neuropathologic changes *in vivo* (Vienbergs *et al*., 19999) and in a hippocampal slice culture (Teter *et al*., 1998). Evidence suggests that apoE is a stress protein (Einstein *et al*., 1995; Maquire *et al*., 1996) which is expressed after acute brain injury due to global hypoxia/ischemia, hypoglycaemia and status epilepticus (Nicoll *et al*., 1996).

Recent findings have demonstrated a significant association between the ε4 allele and late onset familial and sporadic AD (Corder *et al*., 1993; Saunders *et al*., 1993; Poirier *et al*., 1993b, Rebeck *et al*., 1993). The ε4 allele increases the risk and lowers the age of onset distribution, so that patients with an ε4 allele develop AD at an earlier age (Hyman *et al*., 1996; Blacker *et al*., 1997). In a population-

based incidence study, apoE4 homozygotes had a more than 10-fold higher risk of dementia compared with E3 homozygotes, and around 20 per cent of dementia cases were attributable to apoE4 (Slooter *et al*., 1998). ApoE4 may also reduce the age of onset of AD in individuals with DS (Schupf *et al*., 1996; Prasher *et al*., 1997). On the other hand, the $\varepsilon 2$ allele appears to lower the risk and increase the age of onset distribution.

A multitude of mechanistic pathways may jointly contribute to the isoform-specific pathogenic effects of ApoE4:

- ApoE4 accelerates the rate of cognitive decline in nondemented individuals (Reed *et al*., 1994; Helkala *et al*., 1995; Blesa *et al*., 1996; Jonker *et al*., 1998).
- Clinically normal apoE4 subjects in their 50s and 60s exhibit significant reductions of brain metabolic rates for glucose (Small *et al*., 1995; Reiman *et al*., 1996). In AD, however, apoE4 does not appear to be associated with a lower glucose utilization (Corder *et al*., 1997; Higuchi *et al*., 1997; Hirono *et al*., 1998).
- ApoE4 promotes incipient AD pathology in nondemented elderlies (Warzok *et al*., 1998). Remarkably, initial neurofibrillary changes can be found in apoE4 individuals as early as in their 30s (Ghebremedhin *et al*., 1998).
- AD patients with ApoE4 may have a lower brain atrophy in relation to their cognitive status, which was thought to indicate an ApoE4-dependent process which induces neuronal dysfunction before overt brain tissue loss becomes manifest (Yasuda *et al*., 1998).
- ApoE4 may predispose AD patients to particularly low regional cerebral perfusion (Lehtovirta *et al*., 1998).
- ApoE4 may be associated with reduced cholinergic function in normal and AD brains (Soininen *et al*., 1995; Beffert and Poirier, 1996; Allen *et al*., 1997, not confirmed by Svensson *et al*., 1997; Jøgensen and Mogensen, 1997), and was reported to be associated with a more pronounced loss of metabolic activity of cholinergic nucleus basalis neurons (Salehi *et al*., 1998).
- ApoE4 increases amyloid load in the AD brain (e.g. Rebeck *et al*., 1993; Schmechel *et al*., 1993; Beffert and Poirier, 1996; Hyman *et al*., 1996) and DS brain (Hyman *et al*., 1995). This phenomenon may be related to an isoform-specific binding of apoE4 and Aβ. ApoE4 binds less efficiently to Aβ than apoE2 and 3 (LaDu *et al*., 1994; Zhou *et al*., 1996; Aleshkov *et al*., 1997) and hence may accelerate Aβ fibrillization (Wisniewski *et al*., 1994), and fail to exert the protective actions of ApoE3 to Aβ toxicity (Jordan *et al*., 1998), respectively.
- ApoE4 inhibits or fails to support neurite outgrowth (Nathan *et al*., 1994) by a receptor-mediated effect (DeMattos *et al*., 1998) and this effect may be mediated by blockade of microtubule formation (Pitas, 1996). In the presence of a lipid source, expression of human apoE4 blocks, while apoE3 increases neurite outgrowth from murine neuroblastoma cells (Bellosta *et al*., 1995).
- ApoE4 binds to microtubule-associated proteins less avidly than apoE3, which may result in isoform-specific effects on PHF and NFT formation (Strittmatter *et al*., 1994; Huang *et al*., 1994; Fleming *et al*., 1996) which, however, do not appear to result in quantitative differences in the AD brains (Hyman *et al*., 1996).
- ApoE4 aggravates the abnormalities of membrane phospholipid metabolism in AD brains (Klunk *et al*., 1998).
- ApoE4-complexed Aβ is readily sequestered by capillaries and taken up by the brain *in vivo*, while complexes with ApoE2 or 3 have negligible effects (Martel *et al*., 1997).
- Apo E isoform specifically has antioxidant activity, apoE4 being less potent than E3 and E2 (Miyata and Smith, 1996), thus rendering CSF more susceptible to oxidative stress (Beisiegel *et al*., 1997).
- ApoE complexed with Aβ enhances Aβ-induced Ca^{2+} increases in neurons and astrocytes through P/Q type Ca^{2+} channels and this effect is isoform-specific, E4 being significantly more effective than E3 (Wustenberg *et al*., 1997; Muller *et al*., 1998). Similarly, an ApoE fragment, which is also found in human brain, isoform-specifically elevated cytoplasmic Ca^{2+} in cortical and hippocampal cultured neurons both by mobilization of intracellular and influx of extracellular Ca^{2+} (Marques *et al*., 1996; Wang and Gruenstein, 1997; Tolar *et al*., 1997). Addition of protease inhibitors attenuated the neurotoxicity of apoE since the proteolytic fragment was more neurotoxic than full-length apoE (Marques *et al*., 1997).
- Finally, ApoE also may have impacts on immunological processes. Isoform-specifically, apoE enhances complement activation by Aβ (McGeer *et al*., 1997). ApoE genotype appears to be an important determinant of microglial activity:

ApoE4 gene dose significantly increased the number of scattered microglial cells (Saitoh *et al*., 1997) and markers of microglial activation in AD brains (Egensperger *et al*., 1998). On the other hand, apoE3 but not apoE4 blocked activation of microglia by APP metabolites (Barger and Harmon, 1997). ApoE may also modulate the specific immune defence as evidenced by the findings that apoE4 is a risk factor for herpes simplex virus (HSV) type 1 infection (Itzhaki *et al*., 1997) and that ageing and stressed apoE-deficient mice have increased levels of autoantibodies to neuronal antigens (Zhou *et al*., 1999).

ApoE isoform-specific effects are not specific for AD. Repeatedly (e.g. Myers *et al*., 1996; Hofman *et al*., 1997; Katzman *et al*., 1997; Marin *et al*., 1998), but compared to AD less consistently (e.g. Pirttila *et al*., 1996), apoE4 was also suggested as risk factor for vascular dementia, with the larger studies confirming the association. ApoE4 is associated with an increased risk for cardiovascular morbidity and mortality, also in AD patients (Kosunen *et al*., 1995; Olichney *et al*., 1997). ApoE4 genotype modulates the risk for a variety of dementing illnesses and may confer an increased risk for dementia after stroke (Kokmen *et al*., 1996; Slooter *et al*., 1997), dementia associated with normal pressure hydrocephalus (Nacmias *et al*., 1997), for both earlier onset and manifestation of frontal lobe dementia (Minthon *et al*., 1997; Stevens *et al*., 1997), for traumatic encephalopathy associated with boxing (Jordan *et al*., 1997), cognitive decline after cardiac operations (Tardiff *et al*., 1997), senile plaques in temporal lobe epilepsy (Gouras *et al*., 1997), HIV-related dementia (Corder *et al*., 1998), worse outcome after traumatic brain injury (Teasdale *et al*., 1997; Friedman *et al*., 1999), mortality after intracerebral hemorrhage (Alberts *et al*., 1995) and cerebrovascular disease in end-stage renal disease patients (Lim *et al*., 1997). In Creutzfeldt-Jakob disease (CJD) apoE4 is reported to be a risk factor (Amouyel *et al*., 1994), while in sporadic amyotrophic lateral sclerosis (ALS) apoE4 was related to an earlier onset, and more severe clinical presentation and prognosis (Moulard *et al*., 1996). Similarly, apoE4 may be associated with an earlier onset and apoE2 with a later onset of Parkinson's disease (Zareparsi *et al*., 1997). In general, the apoE4 genotype is associated with an increased vulnerability to and an impaired recovery from a variety of brain injuries (Roses and Saunders, 1997). In apoE $\varepsilon 4$ carriers, this increased disposition to neuronal degeneration was highlighted by the finding of a reduced hippocampal volume as early as in their 40s (Tohgi *et al*., 1997) and the occurrence of neurofibrillary changes as early as in their 30s (Ghebremedhin *et al*., 1998).

ApoE, as cholesterol carrier, modulates the production of steroid hormones by which it is regulated itself (Reyland *et al*., 1991). ApoE regulates glucocorticoid (GC) synthesis (Hammami *et al*., 1991), but for the time being it can only be speculated about an ApoE isoform-specific regulation of GC production. Remarkably, apoE deficient mice showed a blunted initial stress response with lower GC levels (Gordon *et al*., 1996; Zhou *et al*., 1998), but higher baseline levels and stronger GC response upon repetitive stress (Zhou *et al*., 1998). The complex interrelationship between the two risk factors stress/GC (see below) and apoE is epitomized by the finding that lack of apoE in knockout mice induces a cognitive deficit but protects heterozygous mice from stress-related cognitive impairment and improves cognitive performance in stressed homozygous mice (Grootendorst *et al*., 1998). ApoE isoform modulates the relative, gender-related risk for familial and sporadic AD (Poirier *et al*., 1993b; Payami *et al*., 1996), and the protective action of oestrogen replacement (van Duijn *et al*., 1996). On the other hand, apoE expression is regulated by oestrogen (Srivastava *et al*., 1996). ApoE polymorphism-mediated alterations of the steroid hormone balance may underly in part the immunological and metabolic phenomena observed in ageing and AD.

Gender

Repeatedly, gender-specific differences in the prevalence/incidence and remaining lifetime risk of AD have been reported, the life expectancy-corrected incidence in women being higher (Silverman *et al*., 1994; Seshadri *et al*., 1997; Gao *et al*., 1998). In DS, women may also exhibit both a higher incidence of clinical AD and a severe phenotypic expression of AD pathology (Raghavan *et al*., 1994). According to another study, male DS patients may have an increased risk of AD (Schupf *et al*., 1998). As multifactorial as the etiopathogenesis of AD may be the determinants of a different sex-related risk. Discussion of these factors clearly deserves a broader frame (Heininger, in preparation). Here, only some general principles will be covered briefly. After correction for selective survival due to a different life expectancy, different odds ratios to contract AD

may be due to a variety of putative pathophysiological variables with sometimes opposite trends on risk status such as X chromosome-associated allelic associations (Zubenko *et al*., 1998b), susceptibility to apoE genotype (Payami *et al*., 1996; Martinez *et al*., 1998, but see Combarros *et al*., 1998a), cerebral perfusion (Akiyama *et al*., 1997; Jones *et al*., 1998), stress responsivity (Seeman *et al*., 1995; Kiecolt-Glaser *et al*., 1997), association of hormonal status and memory performance (Oxenkrug *et al*., 1989; Seeman *et al*., 1997), education, and life style. Of high relevance is a different time course of ageing-related hormonal decline, being gradual in men and more abrupt in women (Lamberts *et al*., 1997). Endocrinologically and metabolically, the menopause elicits a drastic change (Richardson, 1993; Spencer *et al*., 1997), affecting not only gonadal but also thyroid, somatotropic and adrenal hormone levels substantially (Bottiglioni *et al*., 1983; Van Cauter *et al*., 1996; Bernardi *et al*., 1998). Thus, reproductive senescence predicts cognitive decline in aged female monkeys (Roberts *et al*., 1997). These changes may be accelerated by surgically-induced menopause, as suggested in humans (Nappi *et al*., 1999) and rodents (Gibbs, 1998), resulting in an increased incidence and earlier onset of AD (Hong-Goka and Chang, 1997, Nee and Lippa, 1999). As confounding factor, the response of neurons to gonadal steroid deprivation and replacement appears to be sexually dimorphic (Miranda *et al*., 1999).

Other genetic influences

Other genetic factors, though actually less well defined, have been reported to modulate the risk for AD.

A polymorphism in the regulatory region of the apoE gene may be associated with an increased risk of AD independent of the apoE4 allele (Bullido *et al*., 1998; Lambert *et al*., 1998). A polymorphism in exon 3 of the low-density lipoprotein receptor-related protein (LRP) gene is a risk factor for late-onset AD, again independent of apoE4-associated risk (Kang *et al*., 1997; Hollenbach *et al*., 1998). Since LRP is an apoE receptor, this association as well as another with a lipoprotein lipase mutation (Baum *et al*., 1999) points further at an abnormality of lipoprotein metabolism in AD. A deletion in the gene of α_2-macroglobulin, another ligand of the LRP, may also bear a risk for the manifestation of the disease (Blacker *et al*., 1998). A dinucleotide microsatellite allele flanking the α_1-antichymotrypsin gene may modulate the apoE-related risk (Morgan *et al*., 1997). Another apolipoprotein, CI, has been reported to confer an increased risk with its A allele (Poduslo *et al*., 1998).

In keeping with the role of immune mechanisms in the pathophysiology of AD, antigens of the HLA immune recognition system may also modulate the risk. Earlier onset of age is associated with the HLA-A2 allele (Payami *et al*., 1997; Combarros *et al*., 1998b; Ballerini *et al*., 1999). In the absence of apoE4, antigens DR1, 2, or 3 may increase the risk while DR4 or 6 may lower the risk for AD (Curran *et al*., 1997).

Transferrin C2, a variant of the iron transport protein, appears to be weakly associated with AD, emphasizing the role of oxidative stress in the pathophysiology of the disease (van Rensburg *et al*., 1995; Namekata *et al*., 1997).

Other genetic associations include the short variant of the polymorphism within the promoter region of the serotonin transporter gene (Oliveira *et al*., 1998) and a missense mutation of the neurotrophin-3 gene, which was reported to be more frequent in Japanese AD patients than controls (Kunugi *et al*., 1998). Frameshift mutations due to inaccurate interpretation of intact genetic information, failure of the RNA surveillance system and translation into +1 proteins have been shown for APP and ubiquitin-B (van Leeuwen *et al*., 1998). This type of mutation, however, appears to be a more general feature of ageing (Evans *et al*., 1995).

Additional genomic associations can be expected. A complete genomic screen in families affected with late-onset AD revealed an additional locus on chromosome 12 associated with an increased risk for AD (Pericak-Vance *et al*., 1997). Further allelic associations were detected in a systemic survey of the human genome (Zubenko *et al*., 1998a).

MEDICAL RISK FACTORS

Between the genetic and environmental risk factors, the medical risk factors occupy an intermediate position, since often they are already the composite result of genetic and environmental factors.

Traumatic brain injury

Though inconsistent in individual studies (Gentleman and Roberts 1991; Mayeux *et al*., 1993; Katzman and Kawas, 1994; Kondo *et al*., 1994; Rasmusson *et al*., 1995), a meta-analysis found

traumatic brain injury (TBI) to be associated with an increased risk of AD (Mortimer *et al*., 1991). Closed head injury in young adulthood may predict cognitive impairment 50 years later and be associated with a higher AD incidence (Havlik *et al*., 1998). TBI with loss of consciousness >5 min within the preceding 30 years was associated with AD (Schofield *et al*., 1997a). Evidence suggests that the risk is highest for head injuries that occurred after age 70 (Mayeux *et al*., 1993) and, in elderlies 70 years or older, major head injuries predicted an accelerated cognitive decline (Luukinen *et al*., 1999). Similarly, in individuals with the apoE4 genotype the TBI-related risk may be increased (Mayeux *et al*., 1995; Nicoll *et al*., 1995) which, however, was not confirmed by another study (O'Meara *et al*., 1997). Dementia pugilistica following repeated head blows during boxing shares many behavioural, neurophysiological, neurochemical and pathomorphological features of AD (reviewed by Mendez 1995).

TBI may predispose for AD either by reducing the brain reserve in a single event and/or by inducing a long-term process altering neuronal circuitry, excitability and metabolism. TBI is almost invariably associated with neuronal metabolic stress following secondary ischemia (Jenkins *et al*., 1989; Siesjo *et al*., 1995; Martin N.A. *et al*., 1997), cortical spreading depression (Hossmann, 1996; Mayevsky *et al*., 1996), and resulting excitotoxic exposure (Faden *et al*., 1989; Yamikami and McIntosh, 1989; Nilsson *et al*., 1990). These pathophysiological cascades result in regional brain and mitochondrial Ca^{2+} elevation, oxidative stress, dysfunction of oxidative phosphorylation and ATP decrease (Nadler *et al*., 1995; Awasthi *et al*., 1997; Xiong *et al*., 1997). Neuronal and axonal injury-induced metabolic stress is associated with increased APP expression as part of an acute phase response to the TBI (Gentleman *et al*., 1993; Pierce *et al*., 1996). Activation of invading monocytes/macrophages and resident microglial cells occurs with interleukin-1α expression which is correlated with neuronal APP upregulation (Griffin *et al*., 1994; Holmin *et al*., 1998). Deposits of Aβ were found in the brains of some 30 per cent of patients with fatal TBI (Roberts *et al*., 1991; Graham *et al*., 1995). Notably, the likelihood of Aβ deposition and neurobehavioural deficits increased with age (Hamm *et al*., 1992). Possibly, the trauma-associated, glucocorticoid- and prostaglandin-mediated inhibition of macrophage phagocytosis may provide the tissue milieu that is permissive to the accumulation of amyloid deposits (Faist *et al*., 1996; Heininger, 1999b).

TBI, of even low intensity, puts the neurons under metabolic stress with decreased glucose utilization (Hayes and Dixon 1994; Queen and Feeney, 1996) and metabolic depression (Dietrich *et al*., 1994). The cholinergic system undergoes profound degenerative changes following TBI. In the human traumatized brain, markers of cholinergic neurotransmission are lost (Murdoch *et al*., 1998). The loss of cholinergic forebrain neurons after TBI (Leonard *et al*., 1994; Schmidt and Grady, 1995) leads to a disruption of the septohippocampal and basalocortical pathway (DeAngelis *et al*., 1994; Leonard *et al*., 1997) which is of utmost importance for cognitive processes. Thus, even in the absence of overt cognitive deficits, mild TBI animals showed an increased sensitivity to anticholinergic challenge which persisted after moderate TBI (Dixon *et al*., 1995).

According to preclinical, clinical and radiological findings both subacute, but persisting and chronic processes may ensue which compromise neuronal circuitry and function and lay the ground for the susceptibility of TBI patients (and ischemia patients, see below) for AD. Profound and prolonged impairments of cognition occur following experimental TBI and ischemia models (Lyeth *et al*., 1990; Volpe *et al*., 1992; Wood *et al*., 1993; Pierce *et al*., 1998) and human head trauma (Prigatano and Schachter, 1991; Kay *et al*., 1992; Carlesimo *et al*., 1997). In animal models, TBI and even subthreshold mechanical injury to the brain induce persistent neurofilament loss (Posmantur *et al*., 1994) and cytoskeletal pathology (Kanayama *et al*., 1996; Takeda *et al*., 1997). A state of chronic stress is evidenced by chronic APP overexpression (Ciallela *et al*., 1998). Transient ischemia, which is a routine concomitant of TBI, elicits long-term changes with hyperexcitability in rat neocortex and hippocampus due to down-regulation of inhibitory GABAergic function, disturbance of Ca^{2+} regulation (Tsubokawa *et al*., 1992; Akaike, 1995; Luhmann *et al*., 1995; van den Pol *et al*., 1996; Yang and Benardo, 1997), progressive neurotransmitter receptor imbalances (Araki *et al*., 1992), chronic depression of glucose metabolism (Beck *et al*., 1995), and persistent microglial activation (Hsu *et al*., 1994) resulting in long-term degenerative changes (Mudrick and Baimbridge, 1989; Onodera *et al*., 1990; Hsu *et al*., 1994). Similarly, a single systemic dose of the excitotoxin kainic acid induced long-term accumulation of Ca^{2+} in the rat hippo-

campus (van den Berg and Gramsbergen, 1993). Furthermore, transient ischemia leads to iron deposition in the cortex and hippocampus, followed by late-onset and persistent lipid peroxidation resulting eventually in neuronal damage (Kondo *et al*., 1997). Thus, a chronically progressive degenerative process evolves which leads to ongoing axonal degeneration, increasing cytoskeletal abnormality (Takeda *et al*., 1997; Pierce *et al*., 1998), progressive loss of cortical and hippocampal tissue and reactive astrocytosis (Smith D. H. *et al*., 1997; Pierce *et al*., 1998). A reduction of thyroid endocrine function after head trauma may contribute to the development of brain pathology (Mocchegiani *et al*., 1995).

Patients with even mild TBI may exhibit abnormal local cerebral metabolic rates correlating with long-term behavioural and cognitive deficits (Ruff *et al*., 1994; Gross *et al*., 1996). Subacutely developing hippocampal volume atrophy correlates with cognitive decline in the chronic recovery phase of TBI (Bigler *et al*., 1997). As a consequence, TBI in young adulthood exacerbates cognitive decline in the following 30 years (Corkin *et al*., 1989) and may facilitate the evolution of cognitive impairment and AD 50 years later (Havlik *et al*., 1998). The no-effect threshold may be very low since, even with mild brain trauma, up to 35 per cent of victims may show cognitive sequelae (Bohnen and Jolles, 1992). Persistent abnormalities of the cholinergic system may be causally related to the cognitive deficits as suggested by the therapeutic benefit of a cholinergic agonist (Cadenas *et al*., 1994).

Cerebral perfusion

The traditional concept assumes that AD and vascular dementia (VD) are two distinct entities. Due to epidemiological evidence that vascular risk factors which are associated with a reduced cerebral blood flow contribute to the pathophysiology of AD (Crawford, 1996, 1998) this dichotomy has come under scrutiny and has increasingly been questioned (Gold *et al*., 1998; Stewart, 1998). The commonness of vascular abnormalities in AD (Ellis *et al*., 1996; Buee *et al*., 1997; see below) and the rarity of isolated cerebrovascular pathology with dementia at autopsy (Hulette *et al*., 1997; Nolan *et al*., 1998) highlight the dubiousness of this differentiation. Thus, it appears as if AD and VD represent theoretical concepts with heuristic value, but that the clinical reality is characterized by mixed pictures with varying proportions of respective pathologies. Accordingly, a pathophysiological approach indicates that dementing illnesses can be regarded as a continuum with AD and VD representing two more or less abstract poles rather than distinct entities (Heininger, in preparation). A more radical concept even assumes that cerebral capillary perfusion deficits may trigger the pathophysiological AD cascade (Richardson, 1997; de la Torre, 1999).

The cerebrovascular pathology of AD

Processes related to cellular metabolic stress play a predominant role in the pathophysiology of AD. As already pointed out, the brain as the metabolically most active organ is vitally dependent on a steady supply of oxygen and oxidizable substrates. It can be expected that any shortage of this supply, related or unrelated to the AD-specific processes, would aggravate the disease-related metabolic stress and may accelerate the progression of the disease.

As early as 1938, an AD-related cerebrovascular pathology was described (Scholz, 1938). Other reports followed (reviewed by Kalaria, 1996). However, with the emphasis on the neurobiological processes and the often forced delimitation from VD, scientific interest in the vascular aspect of the disease diminished. Only recently, has this interest been revived (see vol. 826 of the *Annals of the New York Academy of Sciences*, which contains a wealth of further reading).

The cerebrovascular bed already undergoes slight changes during ageing (Kalaria, 1996; Buee *et al*., 1997; De Jong *et al*., 1997; Moody *et al*., 1997). These include a decrease in vascular density, number of branches and length of microvessels, luminal narrowing, pericyte degeneration and thickening of the basement membrane. In AD, an aggravation of these changes is frequently observed with both a further decreased density of capillaries and arteriolar multiplications and with coiled, fragmented, and twisted microvessels (Perlmutter and Chui, 1990; Kalaria, 1996; Buee *et al*., 1994, 1997; Moody *et al*., 1997). Moreover, capillary deposits and basement membrane thickening as well as loss of endothelial mitochondria are more pronounced (De Jong *et al*., 1997; Zarrow *et al*., 1997). It can be assumed that these changes are associated with profound haemodynamic consequences, affecting laminar flow and passage of nutrients through the capillary wall (reviewed by de la Torre, 1997b).

AD is very frequently associated with cerebral amyloid angiopathy. Vascular amyloid contains

fibrillar Aβ (Glenner and Wong, 1984). The segments of blood vessels affected by amyloid angiopathy show increased blood–brain barrier permeability, which appears to be due to the disturbed vessel wall structure (Wisniewski *et al*., 1997). Evidence suggests that Aβ causes the cerebral amyloid angiopathy and the degeneration of the cerebral microvasculature (Kalaria, 1997). Vascular smooth muscle cells may be the source of Aβ and amyloid fibrils (Frackowiak *et al*., 1995; Wisniewski *et al*., 1995) and may facilitate the accumulation of Aβ and the assembly of amyloid fibrils (Van Nostrand *et al*., 1998).

Soluble Aβ is vasoactive, induces vasoconstriction *in vivo* and *in vitro* mediated by endothelin, enhances vasoconstriction induced by phenylephrine or endothelin and is toxic to endothelial cells by mechanisms involving Ca^{2+} influx and free radicals (Thomas *et al*., 1996; Crawford *et al*., 1998a; Paris *et al*., 1998a). Aβ may also mediate an auto-amplified inflammatory cascade by upregulating cytokines, expression of adhesion molecules and activators of cellular immune reaction (CD40) in vascular cells (Suo *et al*., 1998). These properties of Aβ are already evident in the pM range and require a random coil or in part β-sheet structure (Crawford *et al*., 1998b). ApoE4 more than apoE3 may enhance the vasoactivity of Aβ and thus could contribute to the vascular component of AD as well (Paris *et al*., 1998b).

Cerebrovascular diseases

Various cardiovascular and cerebrovascular diseases appear to be associated with AD. The pathophysiologic common denominators seem to be both a decreased cerebral perfusion leading to a hypometabolic state (de la Torre, 1997a), lesions reducing the reserve capacity of the brain and, as in head trauma, persistent pathophysiologic processes following the acute event (see above).

Acute and chronic cerebrovascular processes may predispose to the dementias and pave the way to AD (Pasquier and Leys, 1997). Multiple cerebral infarcts are frequently present in AD brains (Nagy *et al*., 1997; Snowdon *et al*., 1997, Heyman *et al*., 1998), often without a clinical history of stroke (Heyman *et al*., 1998). Frequently, stroke patients have reduced cognitive abilities (Tatemichi *et al*., 1996a; Petrovitch *et al*., 1998; Zhu *et al*., 1998a), a faster cognitive decline (Zhu *et al*., 1998b) and are more prone to develop dementia and also AD (Tatemichi *et al*., 1994b; Brayne *et al*., 1998; Pohjasvaara *et al*., 1998; Zhu *et al*., 1998a) with adverse impact for prognosis (Tatemichi *et al*., 1994c; Desmond *et al*., 1998). Subcortical cerebral infarction elicits global and regional cerebral glucose hypometabolism, which correlates with cognitive capacities (Kwan *et al*., 1999). Older age at stroke onset, fewer years of education and concomitant hypoxic-ischemic disorders (e.g. seizures, cardiac arrhythmias, pneumonia) are significant covariates (Tatemichi *et al*., 1994b; Moroney *et al*., 1996; Pohjasvaara *et al*., 1998). Transient ischemic attacks are also a risk factor for accelerating cerebral atrophy, cortico-subcortical perfusion decline and incident dementia (Akiyama *et al*., 1997; Brayne *et al*., 1998). In large survey studies, vascular factors were important risk factors for AD (Brayne *et al*., 1997; Hofman *et al*., 1997) and a cumulative effect of atherosclerosis, white matter lesions (WML) and apoE4 was seen (Hofman *et al*., 1997, Skoog *et al*., 1998a). In other retrospective analyses, cardiovascular and cerebrovascular risk factors were common among AD victims (Tiberghien *et al*., 1993; Tariska *et al*., 1997). Certain stroke features, e.g. dysphasia (Pohjasvaara *et al*., 1998), and particularly lacunar infarcts localized in the basal ganglia, thalamus or deep white matter, predispose to dementia, necessitating fewer neuropathologic AD lesions for manifestation of the disease (Tatemichi *et al*., 1993; Snowdon *et al*., 1997). Accordingly, AD patients with cerebral infarcts or lacunar lesions display a greater overall severity of dementia (Nagy *et al*., 1997; Snowdon *et al*., 1997; Heyman *et al*., 1998).

A marker for atherosclerotic disease, homocysteine (Frishman *et al*., 1998), was found elevated among AD patients (Clarke *et al*., 1998; Lehmann *et al*., 1999), which further confirms the pathophysiological role of atherosclerosis in AD (Miller, 1999).

During normal ageing, cerebral atrophy and WML increase, paralleled by a decline of cerebral perfusion, particularly after age 60 (Claus *et al*., 1996, 1998; Akiyama *et al*., 1997; Meyer *et al*., 1997). WML found in brain imaging studies, or at autopsy, are associated with cognitive impairments and predispose to cognitive deterioration (Pantoni and Garcia, 1997; Meyer *et al*., 1997). WML indicate and are caused by cerebral hypoperfusion (reviewed by Pantoni and Garcia, 1997) and correlate with vascular risk factors (Amar *et al*., 1995) and a history of stroke (Breteler *et al*., 1994b). Although the tissue may attempt to compensate the reduced blood flow by an increased oxygen extrac-

tion (Yamaji *et al*., 1997; Tohgi *et al*., 1998), regions of WML denote areas of decreased levels of energy-rich phosphates (Sappey-Marinier *et al*., 1992). WML are a frequent finding in AD — in neuropathological series up to 60 per cent of patients were affected — and are associated with a more rapid clinical progression (Brun and Englund, 1986; Wallin *et al*., 1989a; Diaz *et al*., 1991). Of note, WML is almost completely absent in early-onset AD, indicating the differential importance of vascular factors in early- versus late-onset AD (Wallin *et al*., 1989a). These differences are also reflected by the pattern of membrane phospholipid changes in early- and late-onset AD (Svennerholm and Gottfries, 1994). The pathophysiologic importance for AD of a reduced cerebrovascular perfusion was highlighted by the transient clinical improvement of a patient after receiving an omental transposition which improved cerebral blood flow (Goldsmith, 1997).

In animal models of chronic cerebral hypoperfusion induced by bilateral occlusion of common carotid arteries, certain features of WML and AD can be mimicked. Cognitive performance is reduced and sensitivity of cognitive performance to muscarinic blockade is increased (de la Torre *et al*., 1997; Farkas *et al*., 1999). Importantly, myelin damage appears to precede the axonal injury (Kurumatani *et al*., 1998). After chronic cerebrovascular insufficiency in adult and aged rats energy stores are depleted, ATP turnover is increased and APP is upregulated (Plaschke *et al*., 1997) paralleled by a decline of regional cytochrome oxidase activity that leads to neuronal apoptosis and memory impairment (Pappas *et al*., 1996; Bennett *et al*., 1998; de la Torre, 1998). Moreover, microvascular abnormalities reminiscent of AD-related changes occur (Farkas *et al*., 1999). It is stressed that the pathophysiological events discussed above with regard to TBI-related ischemia also apply for cerebrovascular ischemic events, thus outlining the processes leading from acute ischemic exposure to delayed and persistent neuronal degeneration. Particularly, the hippocampus is vulnerable to these persistent degenerative changes (Hsu *et al*., 1994).

Cardiovascular disease

Cardiovascular disease (CVD) is associated with AD, leading to a six-fold increased incidence of AD type pathology (Sparks *et al*., 1990; Stewart, 1998). A history of myocardial infarction (MI) increases the risk of probable AD five-fold in older women (Aronson *et al*., 1990), while a history of heart attack is a risk factor for incident dementia (Brayne *et al*., 1998). Importantly, the CVD-associated risk of cognitive decline is increased by apoE4 (Haan *et al*., 1999). CVD is related to poorer cognitive performance and cognitive decline (Breteler *et al*., 1994a; Haan *et al*., 1999). Patients with CVD exhibit accelerated brain ageing with a pattern of hippocampal and cortical intraneuronal Aβ immunoreactivity strikingly similar to AD and DS (Sparks, 1996a), and increased microglial activation (Streit and Sparks, 1997), in severe cases pronounced senile plaque formation and less prevalent NFT densities (Sparks *et al*., 1995; Soneira and Scott, 1996). MI and hypertension are significantly and independently associated with WML (Breteler *et al*., 1994a). Atrial fibrillation is associated with cognitive impairment (Kilander *et al*., 1999), dementia (De Pedis *et al*., 1987) and with AD with cerebrovascular disease (Ott *et al*., 1997). Two separate animal models of CVD show the same pattern of deficits, the severity corresponding to the decreased cardiac output (Sparks, 1996b).

Hypotension and hypertension

Both hypertension and hypotension have been related to the development of dementia including AD (reviewed by Skoog, 1997; Viitanen and Guo, 1997).

Orthostatic hypotension or low blood pressure is a common finding in organic dementia and AD (Guo *et al*., 1996; Passant *et al*., 1997; Pohjasvaara *et al*., 1998; Skoog *et al*., 1998b) which, although causing decreased regional blood flow, may not be clinically symptomatic (Passant *et al*., 1996). Repetitive hypotensive episodes may lead to decreased perfusion pressure of the long penetrating arteries of the deep white matter, induce WML and clinically manifest as cognitive impairment (Raiha *et al*., 1993; Dettmers *et al*., 1997). In line with these findings, low blood pressure was associated with a reduced white matter blood flow in AD patients (Siennicki-Lantz *et al*., 1998). Low blood pressure was associated with decreased cognitive performance 9 years later (Glynn *et al*., 1999). In another longitudinal study, a reduction of systolic blood pressure correlated with cognitive decline (Zhu *et al*., 1998b). In a large cohort of 85-year-olds a low diastolic and systolic blood pressure correlated with frontal and parietal cortical atrophy. Blood pressure decreased further in the

demented and correlated with dementia severity, suggesting that low blood pressure in dementia is mainly a secondary phenomenon (Skoog *et al*., 1998b).

Midlife hypertension was found associated with both AD (Kokmen *et al*., 1991; Kuusisto *et al*., 1997; White *et al*., 1998) and AD with white matter disease (Wallin *et al*., 1989a). Due to a reduced haemodynamic reserve (Fujii *et al*., 1990), hypertension may lead to dementia as a result of ischaemic cerebrovascular events (see above), being the most important risk factor for stroke (Strandgaard and Paulson, 1994). Independent of stroke, in prospective studies of elderly nondemented persons, hypertension was associated with excess cognitive decline (Launer *et al*., 1995; Carmelli *et al*., 1998; Glynn *et al*., 1999; Haan *et al*., 1999; Kilander *et al*., 1999) and accelerated cortical atrophy and cortical perfusion decline (Akiyama *et al*., 1997; Strassburger *et al*., 1997). An animal model of hypertension demonstrated the association of cognitive deficits with degeneration of nicotinic transmission, a marker of ageing and AD (Gattu *et al*., 1997). In longitudinal studies, systolic and diastolic blood pressure were higher in those individuals who developed dementia and AD later (Skoog *et al*., 1996; Guo *et al*., 1997). Notably, the manifestation of dementia appeared to be associated with a decrease in blood pressure (Skoog *et al*., 1996) which continued to decline with increasing dementia severity (Hogan *et al*., 1997; Skoog *et al*., 1998b). This may be a potential source of conflicting data with regard to a blood pressure–cognition relationship (see Viitanen and Guo, 1997). Likewise, cross-sectional and retrospective studies in the elderly indicate that hypertension is associated with cognitive impairment, cognitive decline and cerebral WML (Wilkie and Eisdorfer, 1971; Elias *et al*., 1993; Breteler *et al*., 1994b; Strassburger *et al*., 1997; Carmelli *et al*., 1998; Kilander *et al*., 1999), the latter increasing with duration of hypertension (de Leeuw *et al*., 1998). The diastolic blood pressure appeared to be predictive of cognitive impairment on follow-up (Cacciatore *et al*., 1997). Pathophysiologically, hypertension leads to both a decreased regional glucose utilization, CBF, cerebral oxygen supply and cerebral oxygen consumption in humans and laboratory animals (Wei *et al*., 1992; Nobili *et al*., 1993; Fujishima *et al*., 1995; Salerno *et al*., 1995). Again, apoE genotype may modulate the hypertension-related risk of AD, isoform-specifically (E4 > E3, but not E2) promoting vasoconstriction (Paris *et al*., 1998b). In comparison with CVD patients, hypertension accentuates the occurrence of NFT indicating the metabolic stress of neurons (Sparks *et al*., 1995). Hypertensive rats exhibit a decreased level of polyunsaturated fatty acids in synaptosomal membranes as evidence of a higher level of oxidative stress in these animals compared to normotensive controls (Wei *et al*., 1987, see below).

Therapeutic control of blood pressure may prevent the cognitive impairment, halt the progression of WML (Fukuda and Kitani, 1995; Cacciatore *et al*., 1997), may halt or even reverse the degenerative changes of cerebral microvasculature (Harper, 1987), and reduce the incidence and progression of AD (Guo *et al*., 1999). A recent double-blind controlled drug trial investigated the long-term treatment of hypertension with a calcium antagonist (Staessen *et al*., 1997). After a mean follow-up of 2 years, antihypertensive therapy diminished the incidence of AD by 50 per cent (Forette *et al*., 1998) confirming the pathophysiological role of hypertension in the manifestation of AD and its therapeutic amenability.

Finally, the blood oxygen transportation capacity is an important variable, which together with the perfusion rate determines the total amount of oxygen delivered to the brain. A decrease of this capacity by anaemia also is associated with an increased risk for dementia (Beard *et al*., 1997).

Thyroid disease

Heyman *et al*. (1984) were the first to suggest thyroid disease and hypothyroidism as risk factors for AD in a case-control study. This could not be confirmed by others (Amaducci *et al*., 1986). In the EURODEM meta-analysis of 11 case-control studies, the risk ratio for hypothyroidism was marginally increased (Breteler *et al*., 1991). Furthermore, an elevated TSH, indicative of a hypothyroid state, was associated with an increased odds ratio for dementia in a community-based study (Ganguli *et al*., 1996). Patients with sporadic AD present higher titers for autoantibodies indicating autoimmune thyroid disease (Genovesi *et al*., 1996). Familial AD kindreds display a significant co-segregation between the presence of thyroid autoantibodies and the development of AD (Ewins *et al*., 1991). Similarly, in DS patients, a pattern of abnormal thyroid function is common, often associated with autoimmune thyroiditis (Murdoch *et al*., 1977) and more pronounced in patients with AD manifestations (Percy *et al*., 1990). Cognitive

dysfunction in patients with hypothyroidism is common, particularly in older individuals (Whybrow *et al*., 1969; Jain, 1972; Osterweil *et al*., 1992) and may not be reversible upon therapy (Clarfield, 1988).

Hypothyroidism impairs mitochondrial respiration (Popovici *et al*., 1980; Dembri *et al*., 1983), reduces the activity of enzymes of the TCA cycle and ATP content (Glushakova *et al*., 1976), decreases the rate of glycolysis (Dimitriadis *et al*., 1989), renders mitochondrial function more vulnerable to Ca^{2+} overload (Thomas *et al*., 1987) and reduces the fluidity particularly of mitochondrial membranes (Tacconi *et al*., 1991). Neurobiologically, hypothyroidism causes impairment of signal transduction processes, lysosomal dysfunction, dysregulation of neurotransmitter and energy metabolism (Iriuchijima *et al*., 1991; Sinha *et al*., 1994), reduces slow axonal transport (Stein *et al*., 1991) and causes brain region-specific biochemical dysfunction (Ahmed *et al*., 1993). Thyroid hormones (TH) regulate NGF content and expression of low affinity NGF receptors in adult brain (Calza *et al*., 1997) and, consequently, neurotrophin receptors were decreased in the hypothyreotic rat brain (Alvarez-Dolado *et al*., 1994). Persistent reduction in choline acetyltransferase activity in the basal forebrain of the rat was detected after thyroid deficiency during early life (Patel *et al*., 1987). Given the central role of TH in cholesterol metabolism (Ness, 1991), hypothyroidism may also affect AD development by promoting another risk factor, hypercholesterolaemia (see below).

Hyperthyroidism may also lead to impaired brain mitochondrial energy metabolism, uncoupling of oxidative phosphorylation (Popovici *et al*., 1980), oxidative stress related to the elevated respiratory rate (Satav and Katyare, 1982; Fernandez and Videla, 1993), reduced mitochondrial Ca^{2+} loading capacity, increased mitochondrial Ca^{2+} cycling (Imberti *et al*., 1994) and finally, to mitochondrial permeability transition (Castilho *et al*., 1998). Both hypo- and hyperthyroidism induce low density lipoprotein oxidation (Costanini *et al*., 1998) and may also increase the tissue susceptibility to oxidative challenge, possibly through impairment of the antioxidant capacity (Venditti *et al*., 1997). These abnormalities of energy metabolism may underly the reported reduction in hippocampal dendritic spine density in hyperthyroid animals (Gould *et al*., 1991).

Given the profound effects of thyroid dysfunction on brain tropism and metabolism (Heininger, 1999a), the lack of a stronger association between AD and thyroid disease is hard to reconcile with the mounting evidence that a metabolic deficit plays a key role in the pathophysiology of AD. A possible explanation for this discrepancy may come from an inappropriate definition of hypothyroidism in the aged. In the elderly, subclinical hypothyroidism, characterized by normal free T4 levels and elevated TSH levels, is not uncommon (Drinka and Nolten, 1988). These individuals, though not considered as clinically hypothyroid, have an increased risk to become demented (Ganguli *et al*., 1996) and thus may disguise a stronger thyroid disease/AD relationship. Moreover, the systemic indices give an insufficient picture of the tissue TH state, particularly in the brain. For instance, in the aged even minimal elevations in serum TSH levels are associated with cardial dysfunctions (Cooper *et al*., 1984; Forfar *et al*., 1985) which can be corrected after normalisation of TSH levels (Ridgway *et al*., 1981; Cooper *et al*., 1984). High serum cholesterol and an abnormal pattern of lipoproteins may be sensitive indicators of the tissue level hypothyroid state (Kung *et al*., 1995; Michalopoulou *et al*., 1998). The pattern of therapeutic response of lipid levels to T4 replacement suggests that in the aged individual the 'set point' of hypothalamic–pituitary–thyroid function may be even in the low normal TSH level range (Franklyn *et al*., 1993; Michalopoulou *et al*., 1998). Thus, since the hypothalamic–pituitary leg of the axis is hyporesponsive (Stahelin *et al*., 1982; Cizza *et al*., 1992) already a normal and the more an elevated TSH level may indicate an increased TRH drive and thus hypothyroid CNS state in normal ageing. Finally, as another indicator of suboptimal cerebral TH supply, increased CSF transthyretin levels suggest a compensatory upregulation to counteract the decreased transport of TH to the brain in ageing (Mooradian, 1990).

Depression

The findings from individual case-control studies (e.g. Kokmen *et al*., 1991) were confirmed by the EURODEM Group meta-analysis suggesting a history of late-onset depression as risk factor, increasing the risk for AD independently of family history (Jorm *et al*., 1991; Van Duijn *et al*., 1994). A twin study indicated late-life depression as a risk factor for AD as large as two apoE ε4 alleles (Steffens *et al*., 1997). In addition, a population-based, prospective study suggested early-onset depression as

another risk factor for dementia (Palsson *et al*., 1999). A retrospective follow-up study over 11 years identified depressive symptoms in a very high proportion of patients as initial manifestations (Evenhuis, 1997).

A variety of neurobiological, endocrinological and immunological events related to the manifestation of major depression (MD) may predispose the CNS for AD. Mild to moderate depression may result in decline of specific cognitive abilities (Boone *et al*., 1994; Bassuk *et al*., 1998). This effect appears to be modulated by education, higher education being a protective factor (Palsson *et al*., 1999). MD is associated with ventricular dilation (Jacoby *et al*., 1983; Shima *et al*., 1984; Kellner *et al*., 1986; Schlegel *et al*., 1989) which correlates with cognitive impairment and depressive symptomatology (Kellner *et al*., 1986; Schlegel *et al*., 1989). Moreover, correlating with the duration and age of onset of MD, the hippocampus is atrophic (Axelson *et al*., 1993; Sheline *et al*., 1996). Patients with late-onset MD show a significantly lower whole brain volume, lower tissue density, higher CSF volume and higher ventricle–brain ratio, suggesting a higher degree of central atrophy than in normal aged controls (Jacoby *et al*., 1983; Shima *et al*., 1984; Pantel *et al*., 1997) and also in comparison to aged patients with early-onset MD (Dahabra *et al*., 1998). Notably, both late-onset minor and major depression were associated with prefrontal atrophy which correlated with illness severity (Kumar *et al*., 1998). Other imaging studies detected reduced fronto–temporo–parietal perfusion and increased abnormalities of deep white matter in late onset MD (Lesser *et al*., 1994; Awata *et al*., 1998; Ebmeier *et al*., 1998; Greenwald *et al*., 1998). These WML were associated with cognition deficits and worse antidepressant response (Hickie *et al*., 1995; Leuchter *et al*., 1997; Simpson *et al*., 1997; Awata *et al*., 1998). Conversely, the CBF abnormalities were found reversible after successful treatment (Bench *et al*., 1995; Bonne and Krausz, 1997). Finally, brain functional imaging techniques demonstrated a fronto–temporo-parietal glucose hypometabolism in depressive states (Kumar *et al*., 1993; Biver *et al*., 1994; Mayberg, 1994).

Depression is associated with a variety of neuroendocrinological disturbances (reviewed by Nemeroff and Krishnan, 1991; Holsboer, 1995; Plotsky *et al*., 1995). The HPA axis is dysregulated with elevated plasma cortisol levels which normalize after remission (Steiger and Holsboer, 1997). The dexamethasone suppression test (DST) indicates an impaired HPA axis feedback. Of note, ventricular enlargement and hippocampal atrophy correlated with plasma cortisol, but not impaired DST (Kellner *et al*., 1983; Schlegel *et al*., 1989; Axelson *et al*., 1993), while in elderly depressives the latter correlated with the cognitive impairment (Siegel *et al*., 1989). Likewise, the hypothalamic–pituitary–thyroid axis is hypofunctional (reviewed by Prange *et al*., 1987; Holsboer, 1995). The TSH response to TRH is often blunted, the nocturnal TSH rise absent, transthyretin is reduced in CSF (Hatterer *et al*., 1993; Gorman *et al*., 1997) and euthyroid sick syndrome may be present. Importantly, the peripheral TSH levels are inversely correlated to the global and regional CBF and glucose metabolism (Marangell *et al*., 1997). Other hormonal abnormalities are present which are equally reminiscent of AD-related changes (Heininger, 1999b): (1) nocturnal melatonin levels are reduced in patients with MD and related disorders (Claustral *et al*., 1984; Brown *et al*., 1987; Kennedy *et al*., 1989); (2) seven studies documented decreased CSF somatostatin levels (reviewed by Rubinow *et al*., 1992; (3) insulin resistance is a routine finding (Winokur *et al*., 1988).

The incidence and severity of the MD-related HPA-axis dysregulation increases with age (Asnis *et al*., 1981; Nelson *et al*., 1984). Moreover, the ability for compensatory changes decreases. Thus, in comparison to normal controls, depressed children and adolescents have increased nocturnal melatonin levels (Shafii *et al*., 1996), while in adult and aged depressed these levels are decreased putatively due to CRF-mediated inhibition of melatonin release (Kellner *et al*., 1997). The pattern of endocrinological alterations which has been suggested to be causally related to the MD-related cognitive disturbances (Reus, 1984; Rubinow *et al*., 1984) indicates that the neurons of elderly depressed patients are under metabolic stress. Indeed, in patients with affective disorders, blood cells show a compromise of calcium homeostasis and signalling (and, as a corollary, of energy and antioxidant homeostasis, see Heininger, 1999a), which led to the formulation of the calcium hypothesis of depression (reviewed by Dubovsky, 1994; Heininger *et al*., 1998).

Not surprisingly, these endocrinological abnormalities have profound effects on the immune system of depressed individuals (reviewed by Irwin, 1995). The cellular immune responsivity is blunted (Darko *et al*., 1988). On the other hand, the innate immune system is activated, including an acute phase response with increased plasma levels of

complement components, α-1-antichymotrypsin, α-2-macroglobulin (Song *et al*., 1994a), IL-1 and macrophage activation (Maes *et al*., 1993; McAdams and Leonard, 1993).

Finally, the pathophysiological and putative aetiological relationships between stress (see below) and MD are manifold (reviewed by Akil and Morano, 1995; Post *et al*., 1995) and may represent a common detrimental pathway into AD manifestation.

PSYCHOSOCIAL AND LIFESTYLE RISK FACTORS

Psychosocial stress

Stressful life events may be another risk factor for AD (Henderson *et al*., 1992; Shen, 1992; Bratsun, 1998; Zie *et al*., 1998). Early clinical observations already indicated the relevance of psychological and social adjustment deficiencies (Wang, 1977). Indirect evidence for the pathophysiological role of lifelong stress exposures may be suggested by the premorbid behaviour of social withdrawal. AD patients reportedly exhibit an increased incidence of personality disorders and premorbid personality traits such as psychosocial inactivity, social introversion, pessimism, submissive behaviour and lack of active coping behaviour (Kokmen *et al*., 1991; Kondo *et al*., 1994; Bauer *et al*., 1995; Motomura *et al*., 1996; Malinchoc *et al*., 1997). The intriguing finding of an association of AD with marital status, single individuals having an excess risk (Bickel and Cooper, 1994; Helmer *et al*., 1999), may have a similar basis due to the premorbid personality and behaviours of singles.

AD patients exhibit also biological variables indicating a role of stress exposure and responsivity in the pathophysiology of AD (see Heininger, 1999b). Corticotropin-releasing factor (CRF) and arginine vasopressin neurons in the paraventricular nucleus of the hypothalamus are involved in the regulation of stress responses. These neurons are activated in ageing and AD (Lucassen *et al*., 1993, 1994; Raadsheer *et al*., 1995) and in both chronic stress (Makino *et al*., 1995; Nakase *et al*., 1998; Scott and Dinan, 1998) and depression (Raadsheer *et al*., 1995; Scott and Dinan, 1998), suggesting a continuum of pathophysiological processes (Heinrichs, 1999).

Contemporary stress research emphasizes the importance of the individual appraisal of the stressor. The degree to which the individual can cope with or defend against the stressor determines the individual stress hormone profile and development of stress pathologies (Virgin and Sapolsky, 1997; Bookwala and Schulz, 1998). This variability of coping responses to given stressors, however, makes detection of associations of psychosocial stress exposures with disease risks a cumbersome undertaking. The individual stress vulnerability is modulated very early in life as result of a gene-environment interaction (Bouchard, 1994; Plomin *et al*., 1994; Heim *et al*., 1997). In experimental animals, prenatal and postnatal stress increase HPA-axis responsivity, prolong stress-induced corticosterone secretion in later life (Maccari *et al*., 1995) and impair cognitive performance in vulnerable animals (Lyons *et al*., 1997; Oitzl *et al*., 1997b). On the other hand, postnatal maternal care and neonatal handling reduce HPA reactivity, improve cognitive performance and protect the hippocampus from age-related dysfunction and neuronal loss (Meaney *et al*., 1988; Mohammed *et al*., 1993; Sapolsky 1993; Liu *et al*., 1997).

A variety of conditions associated with elevated GC levels such as chronic stress, depression (see above) and Cushing's syndrome have detrimental sequelae for human brain function and structure (Sapolsky, 1996; Keenan and Kuhn, 1999). Exposure to physiologic stress level GC induces impaired memory performance in healthy human adults (Newcomer *et al*., 1994; Wolkowitz, 1994). In normal aged, GC levels correlate negatively with intellectual performance (Lupien *et al*., 1994; Seeman *et al*., 1995, 1997; Kelly *et al*., 1996) and hippocampal volume (Lupien *et al*., 1998). Longitudinal and cross-sectional studies indicate a memory-deteriorating effect of chronic GC in humans, elderly individuals being particularly susceptible (Keenan *et al*., 1996). War veterans with post-traumatic stress disorder or political prisoners who have been tortured suffer from memory deficits (Sutker *et al*., 1991; Bremner *et al*., 1993; Basoglu *et al*., 1994). Cushing's syndrome is associated with memory impairment, hippocampal atrophy and decreased brain glucose utilization (Starkman *et al*., 1992; Mauri *et al*., 1993; Brunetti *et al*., 1988). Importantly, the pattern of cognitive impairment suggests premature cognitive ageing (Forget *et al*., 1996), increases with age and tends to improve after surgical treatment (Mauri *et al*., 1993). Chronic life stress renders more vulnerable to acute stressful events resulting in an exaggerated sympathetic, neuroendocrine and immune responsivity (Pike *et al*.,

1997). Monkeys in their natural habitat which experience chronic subordination stress and social isolation exhibit hypercortisolism (Sapolsky 1995; Sapolsky *et al*., 1997). A history of low rank pronounced an ageing-related social withdrawal (Veenema *et al*., 1997), a behaviour which has been reported to be associated with AD in humans (see above).

In adult life, exposure to acute and chronic social and psychological stressors worsens cognitive performance in laboratory animals (McEwen and Sapolsky, 1995; Blanchard *et al*., 1995), increases GC levels and impairs hippocampal function and dendritic morphology (Uno *et al*., 1989; McEwen *et al*., 1992; McEwen and Magarinos, 1997). Electrophysiologically, chronic stress or GC accelerate the development of a pattern of ageing-like changes (Landfield *et al*., 1978; Kerr *et al*., 1989, Talmi *et al*., 1993). The stress or ageing-related changes can be prevented by inhibition of GC synthesis and chronic GC receptor blockade (Bodnoff *et al*., 1995; Magarinos and McEwen, 1995; Talmi *et al*., 1996) and mimicked by long-term exposure to GC (Sapolsky *et al*., 1985; Bodnoff *et al*., 1995; Endo *et al*., 1996). The intensity of behavioural and neuroendocrine responses to stressful stimuli determines the rate of ageing and life-span of inbred rodent strains (Gilad and Gilad, 1995). GC, stress and ageing set in motion a vicious cycle leading to a downregulation of hippocampal GC receptors which results in the loss of hippocampal feedback inhibition of HPA-axis activity, increased and/or prolonged GC levels, and hippocampal metabolic endangerment (Sapolsky *et al*., 1984; Zoli *et al*., 1991; Sapolsky,1993; Bennett *et al*., 1996). Mechanistically, GC-elicited glutamate excitotoxicity may be causally involved. Modulatory actions include enhancement of glutamate release and reduction of glutamate reuptake (Armanini *et al*., 1990; Gilad *et al*., 1990; Moghaddam *et al*., 1994; Stein-Behrens *et al*., 1994; Magarinos and McEwen, 1995). Serotonergic mechanisms may equally play a role (Watanabe *et al*., 1992; Luine *et al*., 1993). Importantly, the recovery of GC levels from stress is impaired (Sapolsky *et al*., 1983) and the morphological and electrophysiological effects of stress and GC appear to be more pronounced in aged animals (Kerr *et al*., 1989, Bodnoff *et al*., 1995).

There are multiple, reciprocal relationships between the cholinergic system and the HPA axis. Hippocampal injection of a muscarinic antagonist enhances the HPA axis responsiveness to stress while depletion of hypothalamic ACh resulted in an impaired adaptation to chronic intermittent stress (Ramade and Bayle, 1989; Bhatnagar *et al*., 1997). Conversely, acute stress activates the cholinergic system (Gilad, 1987; Kaufer *et al*., 1998a). Intermediate-term stress elicits mixed responses characterized by decreased choline uptake but an upregulation of muscarinic binding sites (Finkelstein *et al*., 1985; Gonzalez and Pazos, 1992). Chronic GC leads to the degeneration of cholinergic neurons in the medial septal area (Tizabi *et al*., 1989), which may underly the chronic stress-induced enhanced sensitivity to muscarinic antagonists (Kaufer *et al*., 1998b). An increased stress responsivity is associated with a premature degeneration of the cholinergic septohippocampal pathway and shorter life span (Gilad *et al*., 1987). Furthermore, chronic GC administration decreases nicotine sensitivity and brain nicotinic receptor binding in mice, the hippocampal, hypothalamic and frontal cortical regions being particularly sensitive (Pauly *et al*., 1990; Pauly and Collins, 1993). GC also render cholinergic neurons more susceptible to other neurotoxic agents (Hortnagl *et al*., 1993). The glutamatergic system, known to be activated by GC, may participate in the mediation of the degenerative effects (Michel and Agid, 1995). The neurobiological effects are paralleled by behavioural changes. Ten days' stress induced cholinergic hypersensitivity and resistance to scopolamine-induced amnesia, while 30 days' stress resulted in cholinergic hyposensitivity and learning deficits (Zerbib and Laborit, 1990).

Stress also antagonizes the neurotrophin system. Immobilization and cold stress unbalanced the expression of neurotrophins and their receptors in the rat brain (Foreman *et al*., 1993; Ueyama *et al*., 1997). While NGF increased in the cortex and hippocampus, the low-affinity NGF receptor density decreased in the basal forebrain and hippocampus (Foreman *et al*., 1993; Aloe *et al*., 1994). The equally disruptive effects of physiological stress level GC on neurotrophin levels and signal transduction has been discussed earlier (Heininger, 1999a).

Stress may also interact with hormonal activities of other endocrinological axes. Lower postmenopausal oestrogen levels are associated with stress variables as are oestrogen levels during the menstrual cycle and chronic stress may even lead to infertility in women and impotence in men (Selye, 1976; Ballinger, 1990). In young animals the stress-related neurobiological changes could be aggravated by castration and prevented by testosterone

(Mizoguchi *et al*., 1992; Levy *et al*., 1994). Moreover, oestrogen treatment reversed the ageing-related loss of HPA axis feedback inhibition (Ferrini *et al*., 1999) corroborating the importance of protective gonadal hormones (Goodman *et al*., 1996; Heininger, 1999a). Furthermore, chronic stress may decrease the activity of the hypothalamic–pituitary–thyroid axis, a feature which may be attenuated in ageing (Bauer *et al*., 1994; Cizza *et al*., 1995), possibly due to the restricted functional capacity of the axis (Cizza *et al*., 1992). Insulin-like growth factor 1 (IGF-1) is suppressed in socially subordinate male baboons (Sapolsky and Spencer, 1997) and the GC-mediated suppression of astroglial IGF-1 expression may play a role in the age-related decline of axonal sprouting (Ye *et al*., 1997; Woods *et al*., 1998). Finally, neuropeptide Y mRNA has been found suppressed following acute stress (Thorsell *et al*., 1998). As an implication of these hormonal alterations psychosocial stressors may increase the vulnerability of cellular antioxidant systems to pathological conditions (Toleikis and Godin, 1995). Chronic stress may be directly involved in AD-specific processes in that GC and stress impair the Ca^{2+}–energy–redox triangle (Heininger, 1999a) and enhance Aβ production (Liu J. *et al*., 1996, 1998).

Stressful events have profound effects on immune parameters (Apanius, 1998; Elenkov *et al*., 1999), depending on the time course of exposures and responses. Chronic stressors decrease lymphocytes and their proliferative response, natural killer cells, monocytes and their phagocytosis (Song *et al*., 1994b; Kanno *et al*., 1997) and induce an acute phase-like pattern of cytokine elevations, including IL-1, II-6 and TNFα (Zhou *et al*., 1993; Chancellor-Freeland *et al*., 1995. Connor and Leonard, 1998), cytokines which stimulate the HPA axis (Sweep *et al*., 1992; Zhou *et al*., 1993; Raber *et al*., 1997). Again, the stress-related effects are more pronounced and prolonged in aged rodents (Odio *et al*., 1987; Lorens *et al*., 1990; Kanno *et al*., 1997).

Chronic stress may also affect the vascular component of AD pathophysiology. Acute psychological stress elevates persistently total and lipoprotein-associated cholesterol levels (Servatius *et al*., 1993; Muldoon *et al*., 1995) and psychosocial stress factors were associated with an atherogenic serum lipid profile (Vitaliano *et al*., 1995). Thus, together with an atherogenic lipid profile, an increased stress response predicted a higher progression of cardiovascular atherosclerosis (Barnett *et al*., 1997). It is speculated that epidemiological studies may underestimate these relationships, since subjects with these risk factors are also at risk to contract other life-threatening diseases such as cancer (Baltrusch *et al*., 1988) or arteriosclerosis (Ely, 1995) which may prevent them from reaching the age to manifest AD.

Lack of education and of life-long cognitive activity

Epidemiology suggests that low education is a risk factor for accelerated memory decline and dementia (Evans *et al*., 1993; Kondo *et al*., 1994; Stern *et al*., 1994; Ott *et al*., 1995; Brayne *et al*., 1997; Zhu *et al*., 1998b; Lyketsos *et al*., 1999). A diagnostic bias, however, related to the sensitivity of the psychometric instruments and the uniformity of threshold values for low and high educated has to be taken into account (Fratiglioni *et al*., 1998; Geerlings *et al*., 1999). A low occupational challenge as further risk factor for AD highlights the equal importance of life-long mental activity as a protective factor (Fratiglioni *et al*., 1993; Stern *et al*., 1994; Bonaiuto *et al*., 1995; Jorm *et al*., 1998). Conversely, premorbid interests and activities were found reduced in patients with Alzheimer's disease as compared to age- and sex-matched controls (Shen, 1992; Friedland *et al*., 1997).

According to a 'use it or lose it' concept, a lifetime use of the brain by continuing education and learning appears to build up a brain reserve capacity which protects against the losses of ageing and eventual contraction of AD (Swaab, 1991; Timiras, 1995; Mortimer, 1997) and even may prevent cognitive impairment despite a widespread AD pathology (Katzman *et al*., 1998; Davis *et al*., 1999). Hence in AD patients with the same level of cognitive impairment, educated individuals exhibit a reduced cerebral metabolism compared with less educated individuals. On the other hand, comparing patients with the same abnormality of cerebral metabolism, the educated have more preserved intellectual abilities (Alexander *et al*., 1997a). Even during AD the verbal competence, in contrast to non-verbal capacities, differentiates between patients with low and high education (Filley and Cullum, 1997). An intriguing finding supports the reserve capacity concept: head circumference and direct brain volume measurements by MRI identified a small brain volume as a risk factor for AD (Mori *et al*., 1997; Schofield *et al*., 1997b). Education, on the other hand, increases brain size (Coffey *et al*., 1999). An interaction between low education and low socioeconomic

rank may confound the reported association of education and AD (Evans *et al*., 1997; Mortimer *et al*., 1998, see above). Since poorer education in general leads to lower socioeconomic status, social subordinance stress may be a cofactor strengthening the association of low education with cognitive ageing and, finally, AD (Mortimer *et al*., 1998). Conversely, individuals at risk for AD are protected independently by higher education and socioeconomic status/lower subordination stress against manifesting the disease (Mortimer *et al*., 1998). Intriguingly, both neuronal activity and stress exposure/coping ability may affect the same neuroendocrinological substrate. Environmental enrichment in adulthood, like neonatal-handling, resulted in a higher hippocampal GC receptor expression, thus promoting the hippocampal feedback inhibition of HPA-axis activity (Mohammed *et al*., 1993).

These data are extended by findings that both enriched early experience at weaning, training in adulthood and even in senescence result in changes of cortical thickness, size of synaptic contacts and number of dendritic spines and branching compatible with an enhanced use-induced plasticity (Diamond *et al*., 1985; Van Gool *et al*., 1987; Rosenzweig and Bennett, 1996). In rodents, environmental enrichment and neuronal activity upregulate growth factors NGF, BDNF and NT-3 (Lindholm *et al*., 1994; Lauterborn *et al*., 1996; Pham *et al*., 1997). Learning and sensorimotor stimulation also increase somatostatin levels in rat brain (Nilsson *et al*., 1995). Neurotrophins act preferentially on active neurons which, for their part, upregulate neurotrophin receptor expression (Tongiorgi *et al*., 1997). Importantly, the joint action of neurotrophins and electrical activity is required to promote dendritic arborization in brain cortex (McAllister *et al*., 1996). Moreover, the activity-dependent secretion of neurotrophins generates further secretion of neurotrophins, thus establishing a positive feedback mechanism which reinforces and stabilizes synaptic connections (Canossa *et al*., 1997). The neuronal trophic response to activation is supported by astroglial, highly potent activity-dependent neurotrophic factors (ADNF) (Gozes and Brenneman, 1996; Bassan *et al*., 1999). Thus, environmental enrichment increases the density of dendritic contacts (Bogdanovic *et al*., 1998), promotes neuronal survival in senescent animals (Kempermann *et al*., 1998) and prevents the ageing-related loss of synaptic connections observed in sensorialy deprived controls (Saito *et al*., 1994).

An interesting *in vitro* model shed light on the interrelation of use-dependent neuronal plasticity and Ca^{2+} homeostasis (Nelson *et al*., 1990). Previous electric stimulation enhanced and strengthened synaptic connectivity between nerve cells and was able to render the neuronal network resistant against the deleterious action of increased calcium levels.

Lack of physical activity

Lack of physical activity has been identified as a risk factor for AD in a prospective study of 7 years' duration (Yoshitake *et al*., 1995; Fujishima *et al*., 1998). Other case-control studies, using retrospective questionnaires, indicated a reduced premorbid physical activity level in dementia and AD patients (Li *et al*., 1991; Henderson *et al*., 1992; Kondo *et al*., 1994; Friedland *et al*., 1997). A variety of features of physical activity (discussed in part 5 of this series) links these intriguing epidemiological findings to the pathophysiological processes of AD.

Diet

Dietary cholesterol clearly can be defined as risk factor for AD which is modulated by apoE polymorphism. In a prospective study, a high intake of saturated fat and cholesterol was associated with an increased risk of dementia, while fish consumption, an important source of polyunsaturated fatty acids protected against dementia and AD (Kalmijn *et al*., 1997). Another study suggested an increased daily intake of kcal as risk factor (Petot *et al*., 1998). Mean total cholesterol and low-density lipoprotein cholesterol levels are significantly higher in AD patients than in elderly controls (Lehtonen and Luutonen, 1986; Giubilei *et al*., 1990; Czech *et al*., 1994; Kuo *et al*., 1998; Sulkava *et al*., 1998) which correlates with apoE4 status (Czech *et al*., 1994; Sulkava *et al*., 1998). Brain cholesterol was also found elevated in AD frontal cortex and in CVD (Sparks, 1997b). The high incidence of hyperlipaemia was equal in individuals with VD and AD (54 per cent versus 56 per cent) (Deplanque *et al*., 1998) arguing for shared pathophysiological pathways (Heininger in preparation). Dietary fat not only increases cholesterol and triglyceride levels in the serum, but also in the brain (Oner *et al*., 1991). Higher intake of saturated and monounsaturated fatty acids and cholesterol is associated with worse cognitive function (Ortega *et al*., 1997) while a diet low in fatty acids and high in fibre is associated with

better cognitive performance and lower mortality (Huijbregts *et al*., 1998). Serum cholesterol levels correlate negatively with cognitive performance in elderlies (Desmond *et al*., 1993; Orengo *et al*., 1996). In aged individuals plasma cholesterol correlates with the presence of white matter lesions (Breteler *et al*., 1994b) and hyperlipidemia is a risk factor for accelerated cerebral atrophy and cortical perfusion decline (Akiyama *et al*., 1997).

Dietary fat can alter membrane lipid composition in rat brain and liver, even without directly affecting serum cholesterol levels (Divakaran and Venkataraman, 1997; Kessler *et al*., 1985; Huertas *et al*., 1992; Kelly *et al*., 1995). Ageing, on the other hand, is associated with profound increases of plasmalemmal, mitochondrial and microsomal membrane cholesterol content and of membrane cholesterol/phospholipid mole ratio in a variety of organs and cell types (Grinna, 1977; Rivnay *et al*., 1979; Nagy *et al*., 1983; Kessler *et al*., 1985; Sugawa *et al*., 1996). Importantly, the asymmetry of cholesterol distribution between exofacial and cytofacial leaflet of synaptic plasma membranes is increasingly lost with ageing (Igbavboa *et al*., 1996). These changes correspond to the reduced membrane fluidity and Na^+,K^+-ATPase activity and increased age-dependent susceptibility to lipid peroxidation (Rivnay *et al*., 1979; Nagy *et al*., 1983; Kessler *et al*., 1985; Viani *et al*., 1991; Mecocci *et al*., 1997). Evidence suggests that the decrease in membrane fluidity and a concomitant inhibition of $Ca^{2+} + Mg^{2+}$-ATPase activity depend both on cholesterol content and on increased lipid peroxidation products (North and Fleischer, 1983; Viani *et al*., 1991; Choi and Yu, 1995; Wood *et al*., 1995).

Changes in plasmalemmal cholesterol content have substantial consequences for cellular Ca^{2+} and energy homeostasis. Enrichment of cholesterol and its oxidized derivatives in membranes greatly enhance basal and stimulated Ca^{2+} influx and decrease $Ca^{2+} + Mg^{2+}$-ATPase activity which jointly result in increased cytosolic Ca^{2+} levels in a variety of cell types (Boissonneault and Heiniger, 1985; Gleason *et al*., 1991; Kutryk *et al*., 1991; Wood *et al*., 1995). Moreover, activities of liver and heart mitochondrial Ca^{2+} transport, cytochrome oxidases, ATPases, electron transport chain, and adenine nucleotide translocase are decreased, leading to reduced oxidative phosphorylation and a reduced pool of exchangeable adenine nucleotides (ATP and ADP) (Divakaran and Venkataraman, 1977; Rogers *et al*., 1980; Cunningham *et al*., 1981; Kopeikina-Tsiboukidou and Deliconstantinos, 1983; Kim *et al*., 1998; Echegoyen *et al*., 1993). These changes can also be elicited by diets. A high cholesterol-containing diet decreased mitochondrial cytochrome oxidase activity in the monkey liver (Cunningham *et al*., 1981) depressed mitochondrial respiration in rat liver (Rogers *et al*., 1980), lowered coenzyme Q10 and increased hydroperoxides in rabbit hepatocyte mitochondria (Ramirez-Tortosa *et al*., 1997), and partially uncoupled respiration and decreased Ca^{2+}-stimulated respiration in swine myocardial mitochondria (Morrison *et al*., 1997). An atherogenic diet leads to a 50 per cent decrease in brain Ca^{2+} ATPase activity (Oner *et al*., 1991). Oxidative stress may accentuate these changes, indicated by the finding that membrane hydroperoxides correlated inversely with mitochondrial coenzyme Q levels (Ramirez-Tortosa *et al*., 1997). Finally, neurotransmitter transport and receptor-mediated signal transduction is impaired by increasing synaptic cholesterol content, the cholinergic stimulation being particularly vulnerable (Crews *et al*., 1983; Kelly *et al*., 1995; Sugawa *et al*., 1996; Denisova *et al*., 1998). Cholesterol and oxycholesterol can modulate receptor function by two distinct mechanisms, by changes of membrane fluidity and/or specific molecular interactions (Gimpl *et al*., 1997). Notably, young animals are relatively resistant to such changes (Kelly *et al*., 1995; Denisova *et al*., 1998).

Reduction of mitochondrial bioenergetics and aberrations of cholesterol metabolism reinforce each other. Underutilized citrates due to inhibited decarboxylation are degraded to acetyl CoA which are the source for all endogenous cholesterol, thus driving *de novo* steroid synthesis (Tanner, 1995). Autochthon *de novo* synthesis is the overwhelming source of brain cholesterol in a variety of mammals, including man (Spady and Dietschy, 1983; Turley *et al*., 1996) and is insensitive to feedback inhibition by the endproduct (Zhang *et al*., 1994). Thus, the increased brain membrane cholesterol may depend in part at least not on dietary cholesterol but on the mitochondrial ageing process itself (Choi and Yu, 1995). Dietary cholesterol, on the other hand, affects brain cholesterol metabolism. Hypercholesterolemia accelerates brain ageing with increased brain cholesterol levels, increased oxidative stress (Sparks, 1997a,b) and microglial activation in rabbits (Streit and Sparks, 1977).

In AD brains membrane defects, characterized by decreased phospholipids and precursors and

increased degradation products have been documented, suggesting an increased phospholipid degradation (Nitsch *et al*., 1992). Mitochondrial membrane fluidity was reduced, putatively secondary to oxidative stress (Mecocci *et al*., 1996a). In contrast to ageing, the membranes in affected AD brain regions, but not from regions not affected, show a decreased cholesterol/phospholipid mole ratio, leading to a reduced membrane bilayer width (Wallin *et al*., 1989b; Mason *et al*., 1993). Membrane bilayer stability is decreased in AD midtemporal cortex, but not cerebellum (Ginsberg *et al*., 1993).

What may be the mechanisms transforming the excess cholesterol content of ageing membranes into the cholesterol deficit in AD membranes? Lipid peroxidation alters the membranes' lipid composition (Viani *et al*., 1991). Oxidative stress as well as ageing results in a decreased membrane fluidity and increased cholesterol/phospholipid ratio (Ghosh *et al*., 1993; Urano *et al*., 1997). The increase in cholesterol may be a cellular defence mechanism to protect the membranes from oxidative damage (Subramanian *et al*., 1993; Jacobsson-Borin *et al*., 1994; Joseph *et al*., 1997). Cholesterol is a weak antioxidant and stabilizer of membrane structure (Gutteridge, 1978; Jacobsson-Borin *et al*., 1994; Vatassery *et al*., 1995, 1997; Denisova *et al*., 1997; Joseph *et al*., 1997). It is suggested that cholesterol is part of the hierarchical antioxidant system (including melatonin, ascorbate, ubiquinol, vitamin E, thiols like glutathione and polyunsaturated fatty acids) which protect cells from the detrimental actions of oxyradicals (Vatassery *et al*., 1995; Denisova *et al*., 1997; Joseph *et al*., 1997; Urano *et al*., 1997). Cholesterol is protected by the first line antioxidants (Urano *et al*., 1997). When this system gets under stress and deficient, cholesterol is oxidized and may get mobilized (Huertas *et al*., 1992), indicating that membrane cholesterol exchanges with exogenous pools when lipid peroxidation occurs. Thus, when oxidative stress is extensive enough, it finally may result in decreased mitochondrial and microsomal membrane cholesterol content (Huertas *et al*., 1992) and increased brain synaptic plasma membrane fluidity (van Rensburg *et al*., 1994; Wood *et al*., 1995). Quantitatively different degrees of the same pathophysiological process, oxidative stress leading to lipid peroxidation, may therefore induce opposite effects on the target variable, the isoprenoid content of biomembranes. Likewise, mobilization of cholesterol by Aβ may contribute to the AD-related increase in membrane fluidity (Wood *et al*., 1998).

Finally, based on fragmentary evidence, a potential link between APP and cholesterol metabolism and function is outlined. The metabolism of both APP and cholesterol is coupled and influences each other. Brain APP metabolites can be modulated by dietary cholesterol, an effect which needs the presence of apoE (Howland *et al*., 1998). Cholesterol increases cellular APP levels, decreases metabolism and release of sAPP (Bodovitz and Klein, 1996; Racchi *et al*., 1997) and enhances amyloidogenic Aβ production (Mizuno *et al*., 1998) and amyloid deposition (Sparks, 1997a). A reduced sAPP metabolism is also achieved by lipoproteins (Nadeau *et al*., 1998). Furthermore, both a disturbed membrane cholesterol and sphingomyelin distribution increase Aβ production (Urmoneit *et al*., 1998), while a depletion of cholesterol inhibits Aβ generation in hippocampal neurons (Simons *et al*., 1998). On the other hand, Aβ decreases the synthesis of various lipids, particularly cholesterol and phospholipids (Koudinova *et al*., 1996; Walters and Austen, 1998). Moreover, Aβ inhibits cholesterol esterification (Koudinov *et al*., 1996a; Liu Y *et al*., 1998), which may be causal to the decreased plasma cholesterol esterification rate in AD and DS (Lacko *et al*., 1983; Knebl *et al*., 1994). Serum LDL and total cholesterol levels correlate with brain Aβ N-42 content in AD patients, again indicating a link between lipid and APP metabolism (Kuo *et al*., 1998). Thus, cholesterol may induce the generation of its own carrier protein and Aβ and cholesterol may interact in a feedback-cycle, whereby Aβ production is upregulated by cholesterol and downregulates cholesterol synthesis. It is speculated that APP and Aβ, in conjunction with apolipoproteins, may serve as lipid transport proteins to direct lipids, particularly cholesterol to cholesterol domains at synaptic sites and stabilize these structures. APP is developmentally regulated and correlated with synaptogenesis (Moya *et al*., 1994; Morimoto *et al*., 1998) and is localized at synaptic plasma membranes (Shigematsu *et al*., 1992; Shimokawa *et al*., 1993). During synaptogenesis cholesterol is enriched in synaptic structures (Surchev *et al*., 1995; Schroeder *et al*., 1995), presumably to stabilize the synaptic formation and reduce lateral shifts of structural components. Aβ is highly lipophilic and as such is secreted, for instance, by hepatoma cells as an apolipoprotein in association with lipoproteins, transthyretin, phospholipids, triglycerides and cholesterol (Koudinov and Koudinova, 1997). In the plasma and CSF, Aβ is associated with both

the apolipoproteins and lipids of high density lipoproteins (Koudinov *et al*., 1996b, 1998b; LaDu *et al*., 1998). Aβ has markedly higher binding affinity for cholesterol than for phosphatidylcholine or fatty acids (Avdulov *et al*., 1997). This capacity may endow APP as integral constituent of synapses a stabilizing, synaptic domain building property. In fact, Aβ increases the free cholesterol content of membranes (Liu Y. *et al*., 1998). Putatively due to this interaction, cholesterol protects neurons from the disrupture of Ca^{2+} homeostasis and neurotoxicity effected by Aβ *in vitro* (Hartmann *et al*., 1994; Zhou and Richardson, 1996) and hence chronic implants in young and old rat brain of cholesterol- or lipid-embedded Aβ are not neurotoxic *in vivo* (Clemens and Stephenson, 1992).

Diet may also have effects on activities of hormonal feedback axes. High fat and carbohydrate consumption can elevate basal and stress-induced HPA activity in young and elderly individuals (Tannenbaum *et al*., 1996, 1997a). In rats, free fatty acids activate the HPA axis as well (Widmaier *et al*., 1995, Tannenbaum *et al*., 1997b) and reduce plasma corticosteroid binding globulin (Haourigui *et al*., 1994), resulting in an overall increase of free GC. Finally, dietary fats and proteins appear to have modulatory effects on the inflammatory acute phase response (reviewed by Hellerstein, 1989) and may thus also affect the immune system component of AD pathophysiology.

Intake of several vitamins have been related to the incidence of cognitive decline and dementia. In a longitudinal and cross-sectional study of 22 years' duration, plasma vitamin A and C levels correlated significantly with various variables of cognitive performance (Perrig *et al*., 1997). A cross-sectional study suggested a correlation between serum vitamin E level and memory performance (Perkins *et al*., 1999). A prospective study with a mean 4.3 years' follow-up period indicated a protective effect of high-dose vitamins E and C supplement (Morris *et al*., 1998). A low vitamin C intake was found associated with poorer cognitive performance (Gale *et al*., 1996). A cross-sectional study reported reduced plasma levels of vitamins A, C and E in AD patients (Foy *et al*., 1999). AD patients had lower serum folate and vitamin B_{12} levels (Clarke *et al*., 1998). In addition, low folate levels were related to worse cognitive performance, a higher incidence of stroke and dementia (Fioravanti *et al*., 1997; Ebly *et al*., 1998; Hassing *et al*., 1999). Elderlies taking a diet containing more carbohydrate, fibre and vitamins (folate, vitamins C, E, and β-carotenes) show a better cognitive capacity (Ortega *et al*., 1997). Dietary intake of antioxidants such as vitamins A, C and E may be protective against loss of cognitive function (Masaki *et al*., 1994; Jama *et al*., 1996; Paleologos *et al*., 1998, but see Mendelsohn *et al*., 1998) and the development of AD (Petot *et al*., 1998). *In vitro*, antioxidant vitamins can attenuate Aβ cytotoxicity (Yallampalli *et al*., 1998). Reduced vitamin B_{12} levels may be secondary, since they were also found in familial AD (McCaddon and Kelly, 1994). Thiamine (vitamin B_1) deficiency has a role in the aetiology of Wernicke's encephalopathy of chronic alcoholics, elicits in animals an impaired cerebral oxidative metabolism (reviewed by Hazell *et al*., 1998) and may be associated with an increased incidence of AD (Pepersack *et al*., 1999). Further mode of actions linking molecular events with preventive effects will be discussed in part 5 of this series.

Further intriguing evidence associated moderate alcohol drinking with a better cognitive performance (Carmelli *et al*., 1999) and lower incidence of AD (Orgogozo *et al*., 1997).

Smoking

In a population-based study, smoking was negatively associated with prevalent AD, over a 3-year follow-up, however, the risk of incident AD was equal between smokers and non-smokers (Wang *et al*., 1999). A meta-analysis of 19 case-control studies (Lee, 1994) showed a strong protective effect of smoking against contracting AD, a finding which was confirmed by later studies (Van Duijn *et al*., 1995; Callahan *et al*., 1996; Hillier and Salib, 1997). In keeping with this notion, neuropathologic studies suggested a diminution of senile plaques and neurofibrillary changes in brains of smokers (Perry and Perry, 1993; Ulrich *et al*., 1997). However, this effect may be specific for AD only, whereas smoking may be a risk factor for VD (Shaji *et al*., 1996). Smoking may even carry the risk of an overall increase of dementing illnesses (Prince M. *et al*., 1994; Cobb *et al*., 1995; Ott *et al*., 1998; Carmelli *et al*., 1999), particularly in the presence of another risk factor for atherosclerotic disease, hypertension (Prince M. *et al*., 1994). Moreover, there may be a dose effect, other case-control studies suggesting heavy smoking as a risk factor for AD (Shalat *et al*., 1987; Joya-Pardo *et al*., 1991; Ott *et al*., 1998; Merchant *et al*., 1999). Accordingly, in one case-control study light smoking protected from AD and stronger smoking increased the risk (Wang *et al*.,

1997), while a longitudinal study suggested a decreased risk among former smokers (Merchant *et al*., 1999). Smoking is associated with premature menopause (Nilsson *et al*., 1997), but since early menopause is associated with a significantly increased risk of AD (van Duijn *et al*., 1994) this could further confound the epidemiological evidence. The argument that the putative smoking effect may be due to a selective survival bias — representing a 'survival of the fittest' selection — (Riggs, 1993) was questioned (Van Duijn *et al*., 1995). Mortality, classification (AD or VD) and selection biases make an evaluation of the association smoking-AD problematic. The inconsistent epidemiological association of smoking and AD may be driven both by the neurobiological benefits of nicotine and the cerebrovascular sequelae of smoking.

The epidemiological data suggesting a protective effect of smoking may have a neurobiological basis. The nicotinergic system is thought to play an important role in cognition (reviewed by Warburton, 1991; Levin and Simon, 1998). Acute or chronic nicotine or nicotine-agonists improve learning and cognitive performance in young and aged animals (Meguro *et al*., 1994; Arendash *et al*., 1995; Buccafusco *et al*., 1996) and human smokers and non-smokers (Pritchard *et al*., 1992; Hasenfratz and Battig, 1994; Algan *et al*., 1997). Both an enhanced attention, information processing and storage may contribute to these effects (Warburton, 1991). Aged smokers may evade the ageing-related diminution of interhemispheric electrophysiological coherence (Knott and Harr, 1997). Nicotine enhances hippocampal synaptic transmission (Gray *et al*., 1996) and glutamatergic transmission by a presynaptic mechanism (Radcliffe and Dani, 1998) and potentiates evoked single cell activity in aged rat prefrontal cortex (Huitron-Resendiz *et al*., 1997). Nicotinic agonists upregulate nicotinic receptors (Benwell *et al*., 1988; Wonnacott, 1990; Yang and Buccafusco, 1994) and chronic nicotine, if initiated before normal age-related decline, even promoted the retention of nicotinic receptor expression in rat hippocampus (Rogers *et al*., 1998). Moreover, nicotine protects neurons against various excitotoxic stressors (Shimohama *et al*., 1996; Kihara *et al*., 1997; Zamani *et al*., 1997) and NGF deprivation (Yamashita and Nakamura, 1996) and attenuated apoptosis in several non-neural cells through a protein kinase C-dependent mechanism (Wright *et al*., 1993). The upregulation of various constituents of the neurotrophic factor system such as IGF-1 (Kito *et al*., 1997), fibroblast growth factor-2 (Kratz *et al*., 1997) and NGF receptor (Terry and Clarke, 1994; Buccafusco *et al*., 1996) expression may contribute to the neuroprotective action.

AD brains display a substantial loss of nicotinic cholinergic receptors at autopsy (Shimohama *et al*., 1986; Whitehouse *et al*., 1986; Nordberg and Winblad, 1986) and *in vivo* (Nordberg *et al*., 1995). Experimentally, lesioning of the cholinergic basal forebrain cells causes degeneration of their target cells in the hippocampus and cortex (Arendash *et al*., 1987; Nanri *et al*., 1997). Administration of nicotine can prevent the cell loss and associated cognitive deficit (Decker *et al*., 1992; Nanri *et al*., 1997). Accordingly, smokers may exhibit an improved cognitive performance (Letenneur *et al*., 1994) and postmortem had a higher density of hippocampal and brain nicotinic binding sites and choline acetyltransferase (Benwell *et al*., 1988; Perry *et al*., 1996) than non-smoking controls. This protective potential may be related to the modulation of APP metabolism by promoting the secretory pathway (Kim S. H. *et al*., 1997) and the blocking of Aβ toxicity (Kihara *et al*., 1997; Kim S. H. *et al*., 1997; Miao *et al*., 1997). Thus, although smoking, due to inherent detrimental effects such as atherosclerosis and premature menopause, is not a feasible protectant against AD, nicotine or nicotinic agonists may have a potential as therapeutic opportunities in AD (Jones *et al*., 1992; Court and Perry, 1994; Parks *et al*., 1996). In fact, a small trial with 4 weeks of transcutaneous nicotine treatment suggested an improvement of attentional performance in AD patients (White and Levin, 1999).

ENVIRONMENTAL AGENTS

Numerous trace elements, including aluminum (Al), cadmium (Cd), copper (Cu), iron (Fe), lead (Pb), mercury (Hg), selen (Se), and zinc (Zn) have been reported to be imbalanced in AD. A comprehensive coverage of this issue is provided by recent reviews (Markesbery and Ehmann, 1994; Olanow and Arendash, 1994).

A putative role of Al in AD has gained widespread attention but has remained controversial despite intense scientific efforts (Savory *et al*., 1996). Since the first report of an elevated bulk brain Al content in AD (Crapper *et al*., 1973, 1976), a multitude of studies both confirmed (e.g. Trapp *et al*., 1978; Ward and Mason, 1987; Corrigan *et al*., 1993) and refuted (McDermott *et al*., 1979; Jacobs *et al*., 1989; Dedman *et al*., 1992; Bjertness *et al*., 1996)

these initial findings. Microprobe studies suggested increased Al in the nuclei or tangle portion of NFT bearing neurons (Perl and Brody, 1980; Good *et al*., 1992; Yumoto *et al*., 1996) which could not be confirmed by others (Jacobs *et al*., 1989; Chafi *et al*., 1991; Lovell *et al*., 1993; Makjanic *et al*., 1998). The content of Al in senile plaques is similarly controversial (Candy *et al*., 1986; Lansberg *et al*., 1992). A role for transferrin in the cerebral uptake of Al has been proposed (Roskams and Connor, 1990) but this was dismissed in a study comparing transferrin Al content *in situ* in AD and control brains (Dedman *et al*., 1992). Plasma Al levels were also found increased (Basun *et al*., 1991).

The public health implications of this issue are related to the environmental exposure to Al in drinking water (McLachlan, 1995). A significant increase in the risk of AD was reportedly associated with an elevated Al content (>111 μg/l) in drinking water in comparison with districts with lower Al (<10 μg/l) exposure (Martyn *et al*., 1989). In one instance, a regional clustering of dementia mortality was ascribed to a high concentration of Al in the drinking water (Frecker, 1991). Supportive findings were obtained in some (Flaten, 1990; Neri and Hewitt, 1991; McLachlan *et al*., 1996) but not in all further studies (Wood *et al*., 1988; Wettstein *et al*., 1991). Confounding factors may be pH, fluoride, Ca^{2+}, and silica content of water, the latter three and neutral pH potentially reducing the risk (Birchall *et al*., 1989; Edwardson *et al*., 1993; Forbes and Agwani, 1994; Jacqmin *et al*., 1994). In a series of papers, increased exposure to Al from drinking water (reviewed by Forbes *et al*., 1995) and occupational exposure to Al (Rifat *et al*., 1990; Bast-Pettersen *et al*., 1994) were associated with impaired cognitive functions. However, in a radiotracer study, the total uptake of Al from drinking water was determined to be less than 1 per cent of the typical daily uptake from food (Priest *et al*., 1998).

The brain is dependent on a steady supply of Fe for normal function (Gerlach *et al*., 1994). Since free Fe is toxic, its bioavailability has to be controlled stringently. Consistently, iron levels have been found elevated in hippocampus, nucleus basalis, and cortex of AD brains (Andorn *et al*., 1990; Jellinger *et al*., 1990; Dedman *et al*., 1992; Richardson *et al*., 1992) but lower in AD plasma (Basun *et al*., 1991). Importantly, loosely bound Fe which is responsible for free radical reactions *in vivo* is elevated (Kala *et al*., 1996) and redox-active Fe and an iron regulatory protein were documented in association with SP and NFT (Smith M. A. *et al*., 1997). The role of iron transport proteins in the brain accumulation of iron has been indicated (Qian and Wang, 1998). Expression of lactotransferrin, an iron scavenger, was greatly upregulated in effected AD brain regions (Kawamata *et al*., 1993; Leveugle *et al*., 1994). Ferritin, which binds and inactivates extracellular iron, similarly increased in AD brains, associated with reactive microglia and NFT (Grundke-Iqbal *et al*., 1990; Jellinger *et al*., 1990; Dedman *et al*., 1992) and was found almost 10 times higher in the cerebrospinal fluid of patients with AD (Kuiper *et al*., 1994; Robinson *et al*., 1997). Both alterations can be regarded as a cellular defence mechanism (Focht *et al*., 1997). Moreover, Fe binding protein p97 levels are elevated in AD patients' sera (Kennard *et al*., 1996) and are associated with reactive microglia in AD brains (Jefferies *et al*., 1996), while the Fe transport protein transferrin is increased in AD frontal cortex (Loeffler *et al*., 1995). The transferrin C2 subtype, which has an increased frequency in malfunctions which are associated with formation of free radicals, was found to be increased in AD patients (van Rensburg *et al*., 1995; Namekata *et al*., 1997; Van Landeghem *et al*., 1998). Of note, ageing-related changes of Fe homeostasis include increase of total rat brain Fe and possibly ferritin (Roskams and Connor, 1994). Since Fe accumulates in dependence of energy and oxidative stress (Romslo, 1975; Fujimoto *et al*., 1982; Castelnau *et al*., 1998), these alterations of Fe homeostasis indicate a status of cellular stress and damage (Ceccarelli *et al*., 1995; Wang *et al*., 1995).

Zn fulfils important functions in neuronal transmission, as a component of catalytic sites of enzymes, as an antioxidant and in a structural capacity (Bettger, 1993; Cuajungco and Lees, 1997). Significant increases and imbalances of Zn in the AD brain tissue and in areas of severe AD histopathology associated with senile plaques have been reported (Thompson *et al*., 1988; Deibel *et al*., 1996; Cornett *et al*., 1998; Lovell *et al*., 1998). Normal (Hershey *et al*., 1984; Ehmann *et al*., 1986) and reduced levels were reported as well (Ward and Mason, 1987). In subcellular compartments of AD brains, Zn was decreased in the nuclear fraction (Wenstrup *et al*., 1990). These changes, although inconsistent, may indicate oxidative stress, since Zn is readily released from its transport protein under oxidative stress (Maret, 1995), but can reduce oxidative stress by displacing redox-active transition metals such as Fe and Cu and, by binding to thiol groups, protect these from oxidation (Bettger, 1993;

Cuajungco and Lees, 1997). In AD patients, an altered Zn homeostasis was also documented in plasma evidenced by a decreased activity of a carrier peptide (Licastro *et al*., 1996).

A possible pathophysiological role of Cu deficiency in AD was suggested by Hartmann and Evenson (1992). Cu was reportedly decreased in AD hippocampus (Deibel *et al*., 1996), but elevated in the rim of senile plaques compared with AD neuropil (Lovell *et al*., 1998). Ceruloplasmin, the Cu transport protein with both antioxidant and oxidant properties (Fox *et al*., 1995) was found depleted in the AD temporal gyrus (Connor *et al*., 1993) but increased in the hippocampus and frontal cortex (Loeffler *et al*., 1996), and increased in AD CSF (Loeffler *et al*., 1994), indicating an acute phase-type response.

Childhood exposure to Pb was suggested as a risk factor for AD (Prince, 1998). Pb may be a predictor of cognitive performance, with high blood and bone levels associated with impaired cognition (Payton *et al*., 1998).

Hg was reported to be increased in AD cortex, nucleus basalis and amygdala and in subcellular fractions of the temporal lobe (Ehmann *et al*., 1986; Thompson *et al*., 1988; Wenstrup *et al*., 1990; Cornett *et al*., 1998). Hg levels were also found increased in AD patients' blood (Basun *et al*., 1991; Hock *et al*., 1998). Potential mechanisms of Hg neurotoxic actions and their putative role in AD have been discussed (Markesbery and Ehmann, 1994). For instance, Hg may induce signal transduction deficits as encountered in AD (Pendergrass *et al*., 1997). Dental amalgam, for instance, is a potential source of Hg (Hahn *et al*., 1990) and brain Hg levels correlated with the number of amalgam restorations (Eggleston and Nylander, 1987). The number of amalgam fillings, however, was not found associated with a lower cognitive performance (Saxe *et al*., 1995). Environmental sources other than dental amalgam are suspected (Hock *et al*., 1998), although not identified.

Se has an important role in the regulation of the general redox balance as part of the antioxidant enzymes Se-glutathione peroxidases (Ursini and Bindoli, 1987; Bettger 1993). Se was found reduced in AD brains (Ward and Mason, 1987; Wenstrup *et al*., 1990).

Modes of neurotoxic actions of trace elements may include modulation of Ca^{2+} homeostasis (Nicotera and Rossi, 1993), induction or enhancement of oxygen radical formation and augmentation of Aβ aggregation. Cellular Ca^{2+} homeostasis may be disrupted by ions of Al (Anghileri and Thouvenot, 1998; Gandolfi *et al*., 1998), Cr (Anghileri and Thouvenot, 1998), Cu, Fe (Richardson *et al*., 1992; Anghileri and Thouvenot, 1998), Hg (Nicotera and Rossi, 1993; Marty and Atchison, 1998), and Pb (Hegg and Miletic, 1997). Oxidative stress is a general toxic mechanism of a variety of transition metal ions (Stohs and Bagchi, 1995). For instance, it can be induced by Fe (Halliwell and Gutteridge, 1992; Bondy *et al*., 1998), Cd (Kumar *et al*., 1996; Sarkar *et al*., 1997), Cu (Multhaup, 1997; Bondy *et al*., 1998), Hg (Lund *et al*., 1993; Hussain *et al*., 1997) and Mn (Halliwell, 1984), while Al (Gutteridge *et al*., 1985; Bondy *et al*., 1998) may not be able to catalyse the free radical formation but enhance the formation elicited by other trace elements. Similarly, the pro-oxidant action of Cd may be mediated by Fe (Casalino *et al*., 1997). Aβ may enhance the trace metal-induced ROS formation (Bondy *et al*., 1998; Dikalov *et al*., 1999). Cd, Fe, Hg, and Zn may modulate sAPP formation, presumably at the α-secretase level (Bush *et al*., 1994b; Bodovitz *et al*., 1995; Smedman *et al*., 1997; Hock *et al*., 1998) and facilitate Aβ toxicity *in vitro* (Schubert and Chevion, 1995). Moreover, Al, Cu, Fe, and Zn were shown to promote Aβ aggregation (Mantyh *et al*., 1993; Bush *et al*., 1994a; Atwood *et al*., 1998). Finally Al and Pb may contribute to the neurofibrillary pathology (Nikowitz, 1975; Abdel-Ghany *et al*., 1993).

GENETIC DISPOSITION OR ENVIRONMENT?

The composite risk to develop AD is characterized by an interaction of genetic and environmental factors (van Duijn *et al*., 1994). The allocation of hierarchical positions has been attempted, rating the risk factors according to their pathophysiological relevance. Twin studies suggest both genetic and environmental risk factors in varying proportions in late-onset AD (Nee *et al*., 1987; Rapoport *et al*., 1991; Breitner *et al*., 1995; Lannfelt *et al*., 1995; Raiha *et al*., 1996; Gatz *et al*., 1997). The modulating role of environmental factors is highlighted by the finding that some monozygotic twin pairs have remained discordant for AD for up to 20 years (Breitner *et al*., 1995). Twin pairs discordant for AD differed in the level of schooling, a higher level carrying a reduced risk (Raiha *et al*., 1988). In late-onset familial AD, the influence of non-genetic factors may be even greater and the degree of heterogeneity larger (Lopez-Alberola *et*

al., 1997). However, these studies, carried out in a shared cultural environment, are inadequate to remove environmental factors due to cultural lifestyles like diet. Clues for such influences could be provided by comparison of epidemiological data from studies in different ethnic groups living in the same environment (Treves *et al*., 1986; Maestre *et al*., 1995; Tang *et al*., 1996; Farrer *et al*., 1997) and from groups with the same ethnic background but differing cultural environments (Hendrie *et al*., 1995a,b; Osuntokun *et al*., 1995a; Kalaria *et al*., 1997; Hall *et al*., 1998; Holder and Warren, 1998). The relatively low prevalence of AD in developing countries may have ethnic and/or environmental causes (Ogunniyi and Osuntokun, 1991; Chandra *et al*., 1998; Hall *et al*., 1998; Liu HC *et al*., 1998). In sporadic AD, studies consistently confirm the biological relevance of the association between apoE4 allele and risk of AD across various ethnic origins living in Western culture environments. However, the association seems stronger in Japanese and weaker in American Africans than in Caucasians (Maestre *et al*., 1995; Tang *et al*., 1996; Farrer *et al*., 1997). In contrast, ethnically similar populations living in different environments such as African Americans and Nigerian Africans exhibit not only different AD prevalences (Hendrie *et al*., 1995b; Hall *et al*., 1998), but also differ grossly in the association of AD with apoE4 (Osuntokun *et al*., 1995a; Hendrie *et al*., 1995a). Similarly, another study suggested that apoE4 is not associated with AD among East Africans (Kalaria *et al*., 1977; Sayi *et al*., 1997). Notably, brains from non-demented elderly East Africans exhibited a number of AD pathomorphological hallmarks quantitatively and qualitatively similar to specimens from elderly US controls (Ogeng'o *et al*., 1996), while brains from elderly Nigerians lacked these changes (Osuntokun *et al*., 1995b). Other not yet identified genetic determinants may account for these differences. The low incidence of AD in African populations contrasts with the high frequency of apoE4 in sub-Saharan African populations which may be as high as 40 per cent and is therefore considered the ancestral apoE isotype (Zekraoui *et al*., 1997). A possible link reconciling these diverse findings comes from the assessment of lipid metabolism. In a Nigerian population the total serum cholesterol values were found low compared to African American and other Western populations (Kesteloot *et al*., 1989). In a population of South African bushmen a particularly high frequency of the apoE4 allele was not associated with higher plasma cholesterol levels (Sandholzer *et al*., 1995). It was suggested (Sandholzer *et al*., 1995) that only if exposed to a Western lifestyle with its hypercholesterolaemic diet (Finchan *et al*., 1987) and lack of physical exercise inherent individual susceptibilities may manifest as burden to develop late-onset disorders such as atherosclerosis and AD (Kamboh *et al*., 1995). The same conclusion is suggested from studies investigating the prevalence of AD in Old Order Amish, a conservative Christian group in North America, which shuns the modern Western lifestyle. Here, a reduced prevalence of cognitive impairment and AD (Johnson *et al*., 1997) does not appear to be due to a reduced apoE4 frequency (Pericak-Vance *et al*., 1996; Holder and Warren, 1998). In this population, which has also a lower cardiovascular mortality (Hamman *et al*., 1981), a low serum cholesterol, despite a diet high in total and unsaturated fat and cholesterol, is thought to be due to vigorous physical activity (Glick *et al*., 1998). It is inferred that these examples highlight the interdependence of genetic and environmental prerequisites: apoE4 confers a risk of AD if coincident with increased cholesterol levels (Czech *et al*., 1994; Jarvik *et al*., 1995; Chandra and Pandav, 1998; Sulkava *et al*., 1998) due to certain environmental factors such as high dietary fat intake, psychosocial stressors and lack of physical activity. The cross-cultural epidemiological data clearly relativate the multiple pathophysiological and clinical abnormalities elicited by apoE4 (see above), as of minor functional relevance in an organism which lacks abundant cholesterol supply. Another intriguing genetic–environmental link associated apoE4 with HSV1 infection (Itzhaki *et al*., 1997; Matsui *et al*., 1998). Neither factor alone increased the risk for AD, however, the combination strongly correlated with AD brain pathology (Itzhaki *et al*., 1997). However, evidence suggests that the expression of HSV DNA may be simply an indicator of an underlying immune response deficit related to an HPA axis dysfunction (Dobbs *et al*., 1993; Sawiris *et al*., 1994; Noisakran *et al*., 1998). The finding that apoE4 is also a risk factor for herpes labialis (Lin *et al*., 1998) may further hint at an association of apoE genotype and immune dysfunction, possibly secondary to an HPA axis dysregulation.

In the familial type AD, genetic factors clearly are of primary importance though even here a less than 100 per cent penetrance (Rossor *et al*., 1996) and a wide variation in age at onset (Bird *et al*., 1996; Lopera *et al*., 1997) point at additional genetic and environmental modulators. These genetic fac-

tors were indicated by an Israeli study showing a significantly higher incidence of early-onset AD in European or American immigrants, than in African or Asian immigrants (Treves *et al*., 1986). On the other hand, in late-onset FAD, a high degree of phenotypic heterogeneity within families which was even more pronounced between families, was attributed to non-genetic influences (Lopez-Alberola *et al*., 1997).

In an individual patient a unique combination of genetic, biographic and sociocultural factors may act together causing the many etiologies/one pathogenesis riddle of AD. However, above all these aetiological considerations, the overwhelming importance of ageing as the most significant risk factor should be borne in mind.

REFERENCES

Abdel-Ghany M, el-Sebae AK, Shalloway D. 1993. Aluminum-induced nonenzymatic phospho-incorporation into human tau and other proteins. *J Biol Chem* **268**: 11976–11981.

Ahmed MT, Sinha AK, Pickard MR, Kim KD, Ekins RP. 1993. Hypothyroidism in the adult rat causes brain region-specific biochemical dysfunction. *J Endocrinol* **138**: 299–305.

Akaike N. 1995. Time-dependent rundown of GABA response in mammalian CNS neuron during experimental anoxia. *Obesity Res* **3**(Suppl. 5): S769–S777.

Akil HA, Morano MI. 1995. In *Psychopharmacology: The Fourth Generation of Progress*, Bloom FE, Kupfer DJ (eds). Raven Press: New York; 773–785.

Akiyama H, Meyer JS, Mortel KF, Terayama Y, Thornby JI, Konno S. 1997. Normal human aging: factors contributing to cerebral atrophy. *J Neurol Sci* **152**: 39–49.

Alberts MJ, Graffagnino C, McClenny C, Delong D, Strittmatter W, Saunders AM, Roses AD. 1995. Apo E genotype and survival from intracerebral hemorrhage. *Lancet* **346**: 575.

Aleshkov S, Abraham CR, Zannis VI. 1997. Interaction of nascent ApoE2, ApoE3, and ApoE4 isoforms expressed in mammalian cells with amyloid peptide β (1–40). Relevance to Alzheimer's disease. *Biochemistry* **36**: 10571–10580.

Alexander GE, Furey ML, Grady CL, Pietrini P, Brady DR, Mentis MJ, Schapiro MB. 1997a. Association of premorbid intellectual function with cerebral metabolism in Alzheimer's disease: implications for the cognitive reserve hypothesis. *Am J Psychiat* **154**: 165–172.

Alexander GE, Saunders AM, Szczepanik J, Strassburger TL, Pietrini P, Dani A, Furey ML, Mentis MJ, Roses AD, Rapoport SI, Schapiro MB. 1997b. Relation of age and apolipoprotein E to cognitive function in Down's syndrome adults. *Neuroreport* **8**: 1835–1840.

Algan O, Furedy JJ, Demirgoren S, Vincent A, Pogun S. 1997. Effects of tobacco smoking and gender on interhemispheric cognitive function: performance and confidence measures. *Behav Pharmacol* **8**: 416–428.

Allen SJ, MacGowan SH, Tyler S, Wilcock GK, Robertson AGS, Holden PH, Smith SKF, Dawbarn D. 1997. Reduced cholinergic function innormal and Alzheimer's disease brain is associated with apolipoprotein E4 genotype. *Neurosci Lett* **239**: 33–36.

Aloe L, Tirassa P, Alleva E. 1994. Cold water swimming stress alters NGF and low-affinity NGF receptor distribution in developing rat brain. *Brain Res Bull* **33**: 173–178.

Alvarez-Dolado M, Iglesias T, Rodriguez-Pena A, Bernal J, Munoz A. 1994. Expression of neurotrophins and the trk family of neurotrophin receptors in normal and hypothyroid rat brain. *Brain Res Mol Brain Res* **27**: 249–257.

Amaducci LA, Fratiglioni L, Rocca WA, Fieschi C, Livrea P, Pedone D, Bracco L, Lippi A, Gandolfo C, Bino G, Prencipe M, Bonatti ML, Girotti F, Carella F, Tavolato B, Ferla S, Lenzi GL, Carolei A, Gambi A, Grigoletto F, Schoenberg BS. 1986. Risk factors for clinically diagnosed Alzheimer's disease: a case-control study of an Italian population. *Neurology* **36**: 922–931.

Amar K, Lewis T, Wilcock G, Scott M, Bucks R. 1995. The relationship between white matter low attenuation on brain CT and vascular risk factors: a memory clinic study. *Age Ageing* **24**: 411–415.

Amouyel P, Vidal O, Launay JM, Laplanche JL. 1994. The apolipoprotein-E alleles as major susceptibility factors for Creutzfeldt-Jakob-disease. *Lancet* **344**: 1315–1318.

Ancolio K, Marambaud P, Dauch P, Checler F. 1997. α-Secretase-derived product of β-amyloid precursor protein is decreased by presenilin 1 mutations linked to familial Alzheimer's disease. *J Neurochem* **69**: 2494–2499.

Andorn MC, Britton RS, Bacon BR. 1990. Evidence that lipid peroxidation and total iron are increased in Alzheimer's brain. *Neurobiol Aging* **11**: 316.

Anghileri LJ, Thouvenot P. 1998. ATP in cellular calcium-overload by trivalent metal ions. *Biol Trace Elem Res* **62**: 115–122.

Apanius V. 1998. Stress and immune defense. *Stress Behav Adv Study Behav* **27**: 133–153.

Arai Y, Suzuki A, Mizuguchi M, Takashima S. 1997. Developmental and aging changes in the expression of amyloid precursor protein in Down's syndrome brains. *Brain Devel* **19**: 290–294.

Araki T, Kato H, Kogure K, Kanai Y. 1992. Long-term changes in gerbil brain neurotransmitter receptors following transient cerebral ischemia. *Br J Pharmacol* **107**: 437–442.

Arendash GW, Millard WJ, Dunn AJ, Meyer EM. 1987. Long-term neuropathological and neurochemical effects of nucleus basalis lesions in the rat. *Science* **238**: 952–956.

Arendash GW, Sengstock GJ, Sanberg PR, Kem WR. 1995. Improved learning and memory in aged rats with chronic administration of nicotinic receptor agonist GTS-21. *Brain Res* **674**: 252–259.

Armanini MP, Hutchins C, Stein BA, Sapolsky RM. 1990. Glucocorticoid endangerment of hippocampal neurons is NMDA-receptor dependent. *Brain Res* **532**: 7–12.

Aronson MK, Ooi WL, Morgenstern H, Hafner A, Masur D, Crystal H, Frishman WH, Fisher D, Katzman R. 1990. Women, myocardial infarction, and dementia in the very old. *Neurology* **40**: 1102–1106.

Asnis GM, Sachar EJ, Halbreich U, Nathan RS, Novacenko H, Ostrow LC. 1981. Cortisol secretion in relation to age in major depression. *Psychosom Med* **43**: 235–242.

Atwood CS, Moir RD, Huang X, Scarpa RC, Bacarra NM, Romano DM, Harshorn MA, Tanzi RE, Bush AI. 1998. Dramatic aggregation of Alzheimer Aβ by Cu(II) is induced by conditions representing physiological acidosis. *J Biol Chem* **273**: 12817–12826.

Avdulov NA, Chochina SV, Igbavboa U, Warden CS, Vassiliev AV, Wood WG. 1997. Lipid binding to amyloid β-peptide aggregates: preferential binding of cholesterol as compared with phosphatidylcholine and fatty acids. *J Neurochem* **69**: 1746–1752.

Awasthi D, Church DF, Torbati D, Carey ME, Pryor WA. 1997. Oxidative stress following traumatic brain injury in rats. *Surg Neurol* **47**: 575–582.

Awata S, Ito H, Konno M, Ono S, Kawashima R, Fukuda H, Sato M. 1998. Regional cerebral blood flow abnormalities in late-life depression: relation to refractoriness and chronification. *Psychiat Clin Neurosci* **52**: 97–105.

Axelson DA, Doraiswamy PM, McDonald WM, Boyko OB, Typler LA, Patterson LJ, Nemeroff CB, Ellinwood EH Jr, Krishnan KR. 1993. Hypercortisolemia and hippocampal changes in depression. *Psychiat Res* **47**: 163–173.

Azari NP, Pettigrew KD, Pietrini P, Horwitz B, Schapiro MB. 1994. Detection of an Alzheimer'sdisease pattern of cerebral metabolism in Down's syndrome. *Dementia* **5**: 69–78.

Ballerini C, Nacmias B, Rombola G, Marcon G, Massacesi L, Sorbi S. 1999. HLA A2 allele is associated with age at onset of Alzheimer's disease. *Ann Neurol* **45**: 397–400.

Ballinger S. 1990. Stress as a factor in lowered estrogen levels in the early postmenopause. *Ann NY Acad Sci* **592**: 95–113.

Baltrusch HJ, Seidel J, Stangel W, Waltz ME. 1988. Psychosocial stress, aging and cancer. *Ann NY Acad Sci* **521**: 1–15.

Bambrick LL, Yarowsky PJ, Krueger BK. 1995. Glutamate as a hippocampal neuron survival factor: an inherited defect in the trisomy 16 mouse. *Proc Natl Acad Sci USA* **92**: 9692–9696.

Barger SW, Harmon AD. 1997. Microglial activation by Alzheimer amyloid precursor protein and modulation by apoliproprotein E. *Nature* **388**: 878–881.

Barnett PA, Spence JD, Manuck SB, Jennings JR. 1997. Psychological stress and the progression of carotid artery disease. *J Hypertens* **15**: 49–55.

Basoglu M, Paker M, Paker O, Ozmen E, Marks I, Incesu C, Sahin D, Sarimurat N. 1994. Psychological effects of torture: a comparison of tortured with nontortured political activists in Turkey. *Am J Psychiat* **151**: 76–81.

Bassan M, Zamostiano R, Davidson A, Pinhasov A, Giladi E, Perl O, Basan H, Blat C, Gibney G, Glazner G, Brenneman DE, Gozes I. 1999. Complete sequence of a novel protein containing a femtomolar-activity-dependent neuroprotective peptide. *J Neurochem* **72**: 1283–1293.

Bassuk SS, Berkman LF, Wypij D. 1998. Depressive symptomatology and incident cognitive decline in an elderly community sample. *Arch Gen Psychiat* **55**: 1073–1081.

Bast-Pettersen R, Drablos PA, Goffeng LO, Thomassen Y, Torres CG. 1994. Neuropsychological deficit among elderly workers in aluminum production. *Am J Ind Med* **25**: 649–662.

Basun H, Forssel LG, Wetterberg L, Winblad B. 1991. Metals and trace elements in plasma and cerebrospinal fluid in normal aging and Alzheimer's disease. *J Neural Transm Park Dis Dement Sect* **3**: 231–258.

Vauer J, Stadtmuller G, Qualmann J, Bauer H. 1995. Premorbid psychological processes in Alzheimer's disease and in vascular dementia. *Zeitschrift Gerontol Geriat* **28**: 179–189..

Bauer M, Priebe S, Kurten I, Graf KJ, Baumgartner A. 1994. Psychological and endocrine abnormalities in refugees from East Germany. 1. Prolonged stress, psychopathology, and hypothalamic–pituitary–thyroid axis activity. *Psychiat Res* **51**: 61–73.

Baum L, Chen L, Maslih E, Chan YS, Ng HK, Pang CP. 1999. Lipoprotein lipase mutations and Alzheimer's disease. *Am J Med Genet* **88**: 136–139.

Beard CM, Kokmen E, O'Brien PC, Ania BJ, Melton LJ III 1997. Risk of Alzheimer's disease among elderly patients with anemia; population-based investigations in Olmsted County, Minnesota. *Ann Epidemiol* **7**: 219–224.

Beck T, Goller HJ, Wree A. 1995. Chronic depression of glucose metabolism in postischemic rat brains. *Stroke* **26**: 1107–1113.

Beffert U, Poirier J. 1996. Apolipoprotein E, plaques, tangles and cholinergic dysfunction in Alzheimer's disease. *Ann NY Acad Sci* **777**: 166–174.

Begley JG, Duan W, Chan S, Duff K, Mattson MP. 1999. Altered calcium homeostasis and mitochondrial dysfunction in cortical synaptic compartments of presenilin-1 mutant mice. *J Neurochem* **72**: 1030–1039.

Beisiegel U, Arlt S, Daher D, Schippling S, Mann U, Muller-Thomsen T, Sturenburg H-J, Buhmann C, Bernhardt R, Mann WA, Kontush A. 1997. Apo-

lipoprotein E genotype determines the lipid level in and oxidizability of human cerebrospinal fluid. *Soc Neurosci Abstr* **23**: 1834.

Bellosta S, Nathan BP, Orth M, Dong LM, Mahley RW, Pitas RE. 1995. Stable expression and secretion of apolipoproteins E3 and E4 in mouse neuroblastoma cells produces differential effects on neurite outgrowth. *J Biol Chem* **270**: 27063–27071.

Bench CJ, Frackowiak RSJ, Dolan RJ. 1995. Changes in regional cerebral blood flow on recovery from depression. *Psychol Med* **25**: 247–261.

Bennett MC, Mlady GW, Fleshner M, Rose GM. 1996. Synergy between chronic corticosterone and sodium azide treatments in producing a spatial learning deficit and inhibiting cytochrome oxidase activity. *Proc. Natl Acad Sci USA* **93**: 1330–1334.

Bennett SAL, Tenniswood M, Chen JH, Davidson CM, Keyes MT, Fortin T, Pappas BA. 1998. Chronic cerebral hypoperfusion elicits neuronal apoptosis and behavioral impairment. *Neuroreport* **9**: 161–166.

Benwell MEM, Balfour DJK, Anderson JM. 1988. Evidence that tobacco smoking increases the density of (^{3}H)nicotine binding sites in human brain. *J Neurochem* **50**: 1243–1262.

Bernardi F, Petraglia F, Seppala M, Spinetti A, Bertolini S, Ferdeghini M, Genazzani AR. 1988. Somatotropic axis and body weight in pre-menopausal women: evidence for a neuroendocrine derangement, in absence of changes of insulin-like growth factor binding protein concentration. *Hum Reprod* **13**: 279–284.

Bettger WJ. 1993. Zinc and selenium, site-specific versus general antioxidation. *Can J Physiol Pharmacol* **71**: 721–724.

Bhatnagar S, Costall B, Smythe JW. 1997. Hippocampal cholinergic blockade enhances hypothalamic–pituitary–adrenal responses to stress. *Brain Res* **766**: 244–248.

Bhaumik S, Collacott RA, Garrick P, Mitchel C. 1991. Effect of thyroid stimulating hormone on adaptive behaviour in Down's syndrome. *J Ment Defic Res* **35**: 512–520.

Bickel H, Cooper B. 1994. Incidence and relative risk of dementis in an urban elderly population: findings of a prospective field study. *Psychol Med* **24**: 179–192.

Bigler ED, Blatter DD, Anderson CV, Johnson SC, Gale SD, Hopkins RO, Burnett B. 1997. Hippocampal volume in normal aging and traumatic brain injury. *Am J Neuroradiol* **18**: 11–23.

Birchall JD, Exley C, Chappell JS, Phillips MJ. 1989. Acute toxicity of aluminum to fish eliminated in silicon-rich acid waters. *Nature* **338**: 146–148.

Bird TD, Levy-Lahad E, Poorkaj P, Sharma V, Nemens E, Lahad A, Lampe TH, Schellenberg GD. 1996. Wide range in age of onset for chromosome 1-related familial Alzheimer's disease. *Ann Neurol* **40**: 932–936.

Biver F, Goldman S, Delvenne V, Luxen A, De Maertelaer V, Hubain P, Mendlewicz J, Lotstra F. 1994. Frontal and parietal metabolic disturbances in unipolar depression. *Biol Psychiat* **36**: 381–388.

Bjertness E, Candy JM, Torvik A, Ince P, McArthur F, Taylor GA, Johansen SW, Alexander J, Gronnesby JK, Bakketeig LS, Edwardson JA. 1996. Content of brain aluminum is not elevated in Alzheimer's disease. *Alzheimer Dis Assoc Disord* **10**: 171–174.

Blacker D, Haines JL, Rodes L, Terwedow H, Go RCP, Harrell LE, Perry RT, Bassett SS, Chase G, Meyers D, Albert MS, Tanzi RE. 1997. ApoE4 and age at onset of Alzheimer's disease: The NIMH genetics initiative. *Neurology* **48**: 139–147.

Blacker D, Wilcox MA, Laird NM, Rodes L, Horvath SM, Go RCP, Perry R, Watson B, Bassett SS, McInnis MG, Albert MS, Hyman BT, Tanzi RE. 1998. α_2-macroglobulin is genetically associated with Alzheimer's disease. *Nature Genetics* **19**: 357–360.

Blanchard DC, Spencer RL, Weiss SM, Blanchard RJ, McEwen B, Sakai RR. 1995. Visible burrow system as a model of chronic social stress: behavioral and neuroendocrine correlates. *Psychoneuroendocrinology* **20**: 117–134.

Blesa R, Adroer R, Santacruz P, Ascaso C, Tolosa E, Oliva R. 1996. High apolipoprotein E ε4 allele frequency in age-related memory decline. *Ann Neurol* **39**: 548–551.

Bodnoff SR, Humphrey AG, Lehmann JG, Diamone DM, Rose GM, Meaney MJ. 1995. Enduring effects of chronic corticsterone treatment on spatial learning, synaptic plasticity and hippocampal neuropathology in young and mid-aged rats. *J Neurosci* **15**: 61–69.

Bodovitz S, Klein WL. 1996. Cholesterol modulates α-secretase cleavage of amyloid precursor protein. *J Biol Chem* **271**: 4436–4440.

Bodovitz S, Falduto MT, Frail DE, Klein WL. 1995. Iron levels modulate α-secretase cleavage of amyloid precursor protein. *J Neurochem* **64**: 307–315.

Bogdanovic N, Pham TM, Petanjek Z, Soderstrom S, Winblad B, Mohammed AH. 1998. Effects of environmental enrichment on nerve growth factor levels and dendritic morphology in elderly rats. *Neurobiol Aging* **19**(Suppl. 4): S289.

Bohnen N, Jolles J. 1992. Neurobehavioral aspects of postconcussive symptoms after mild head injury. *J Nervous Mental Dis* **180**: 683–692.

Boissonneault GA, Heiniger HJ. 1985. 25-Hydroxycholesterol-induced elevations in ^{45}Ca uptake: permeability changes in P815 cells. *J Cell Physiol* **125**: 471–475.

Bonaiuto S, Rocca WA, Lippi A, Giannandrea E, Mele M, Cavarzeran F, Amaducci L. 1995. Education and occupation as risk factors for dementia: a population-based case-control study. *Neuroepidemiology* **14**: 101–109.

Bondy SC, Guo-Ross SX, Truong AT. 1998. Promotion of transition metal-induced reactive oxygen species formation by β-amyloid. *Brain Res* **799**: 91–96.

Bonne O, Krauz Y. 1997. Pathophysiological significance of cerebral perfusion abnormalities in major depression — trait or state marker? *Europ Neuropsychopharmacol* **7**: 225–233.

Bookwala J, Schulz R. 1998. The role of neuroticism andmastery in spouse caregivers' assessment of and response to a contextual stressor. *J Gerontol Ser B — Psychol Sci Soc Sci*: P155–P164.

Boone KB, Lesser I. Miller B, Wohl M, Berman N, Lee A, Palmer B. 1994. Cognitive functioning in a mildly to moderately depressed geriatric sample: relationship to chronological age. *J Neuropsychiat Clin Neurosci* **6**: 267–272.

Borchelt DR, Thinakaran G, Eckman CB, Lee MK, Davenport F, Ratovitsky T, Prada C-M, Kim G, Seekins S, Yager D, Slunt HH, Wang R, Seeger M, Levey AI, Gandy SE, Copeland NG, Jenkins NA, Price DL, Younkin SG, Sisodia SS. 1996. Familial Alzheimer's disease-linked presenilin 1 variants elevate Aβ1–42/1–40 ratio *in vitro* and *in vivo*. *Neuron* **17**: 1005–1013.

Bottiglioni F, de Aloysio D, Nicoletti G, Mauloni M, Mantuano R, Capelli M. 1983. A study of thyroid function in the pre- and post-menopause. *Maturitas* **5**: 105–114.

Bouchard TJ. 1994. Genes, environment and personality. *Science* **264**: 1700–1701.

Bratsun AL. 1998. Risk factors of the development of Alzheimer's type dementias. *Zhu Nevropatologii i Psikhiatrii Imeni S S Korsakova* **98**: 16–20.

Brayne C, Huppert FA, Xuereb JH, Gertz H-J, Chi L-Y, McGee MA, Paykel ES, Harrington C, Mukaetova-Ladinska E, O'Sullivan A, Dening T, Freer C, Wischik CM. 1997. An epidemiological study of the dementias in Cambridge: from clinical progression to neuropathology. In *Alzheimer's Disease: Biology*, *Diagnosis and Therapeutics*, Iqbal K, Winblad B, Nishimura T, Takeda M, Wisniewski HM (eds). John Wiley: Chichester; 11–20.

Brayne C, Gill C, Huppert FA, Barkley C, Gehlhaar E, Girling DM, O'Connor DW, Paykel ES. 1998. Vascular risks and incident dementia: Results from a cohort study of the very old. *Dementia Geriatr Cognit Disord* **9**: 175–180.

Breitner JC, Welsh KA, Gau BA, McDonald WM, Steffens DC, Saunders AM, Magruder KM, Helms MJ, Plassman BL, Folstein MF, Brandt J, Robinette CD, Page WF. 1995. Alzheimer's disease in the National Academy of Sciences–National Research Council Registry of Aging Twin Veterans. III. Detection of cases, longitudinal results, and observations on twin concordance. *Arch Neurol* **52**: 763–771.

Bremner JD, Scott TM, Delaney RC, Southwick SM, Mason JW, Johnson DR, Innis RB, McCarthy G, Charney DS. 1993. Deficits in short-term memory in posttraumatic stress disorder. *Am J Psychiat* **150**: 1015–1019.

Breteler MMB, van Duijn CM, Chandra V, Fratiglioni L, Graves AB, Heyman A, Jorm AF, Kokmen E, Kondo K, Mortimer JA, Rocca WA, Shalat SL, Soininen H, Hofman A. 1991. Medical history and the risk of Alzheimer's disease: a collaborative re-analysis of case-control studies. *Int J Epidemiol* **20**(Suppl. 2): S36–S42.

Breteler MMB, Clauss JJ, Grobbee DE, Hofman A. 1994a. Cardiovascular disease and distribution of cognitive function in elderly people: The Rotterdam Study. *Br Med J* **308**: 1604–1608.

Breteler MMB, van Swieten JC, Bots ML, Grobbee DE, Claus JJ, van den Hout JHW, van Harskamp F, Tanghe HLJ, de Jong PT, van Gijn J, Hofman A. 1994b. Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: the Rotterdam Study. *Neurology* **44**: 1246–1252.

Brook JD, Gasden RG, Chandley AC. 1984. Maternal ageing and aneuploid embryos: evidence from the mouse that biological and not chronological age is the important influence. *Hum Genetics* **66**: 41–45.

Brown RP, Kocsis JH, Caroff S, Amsterdam J, Winokur A, Stokes P, Frazer A. 1987. Depressed mood and reality disturbance correlate with decreased nocturnal melatonin in depressed patients. *Acta Psychiatr Scand* **76**: 272–275.

Brugge KL, Nichols SL, Salmon DP, Hill LR, Delis DC, Aaron L, Trauner DA. 1994. Cognitive impairment in adults with Down's syndrome: similarities to early cognitive changes in Alzheimer's disease. *Neurology* **44**: 232–238.

Brun A, Englund E. 1986. White matter disorder in dementia of the Alzheimer type: a pathoanatomical study. *Ann Neurol* **19**: 253–262.

Brunetti A, Fulham MJ, Aloj L, DeSouza B, Nieman L, Oldfield EH, DiChiro G. 1998. Decreased brain glucose utilization in patients with Cushing's disease. *J Nucl Med* **39**: 786–790.

Buccafusco JJ, Prendergast MA, Terry AV, Jackson WJ. 1996. Cognitive effects of nicotinic cholinergic receptor agonists in nonhuman primates. *Drug Devel Res* **38**: 196–203.

Buee L, Hof PR, Bouras C, Delacourte A, Perl DP, Morrison JH, Fillit HM. 1994. Pathological alterations of the cerebral microvasculature in Alzheimer's disease and related dementing disorders. *Acta Neuropathol (Berl)* **87**: 469–480.

Buee L, Hof PR, Delacourte A. 1997. Brain microvascular changes in Alzheimer's disease and other dementias. *Ann NY Acad Sci* **826**: 7–24.

Bullido MJ, Artiga MJ, Recuero M, Sastre I, Garcia MA, Aldudo J, Lendon C, Han SW, Morris JC, Frank A, Vazquez J, Goate A, Valdivieso F. 1998. A polymorphism in the regulatory region of APOE associated with risk for Alzheimer's disease. *Nature Genetics* **18**: 69–71.

Busciglio J, Yankner BA. 1995. Apoptosis and increased generation of reactive oxygen species in Down's syndrome neurons *in vitro*. *Nature* **378**: 776–779.

Bush AI, Pettingell WH, Multhaup G, Paradis MD, Vonsattel JP, Gusella JF, Beyreuther K, Masters CL, Tanzi RE. 1994a. Rapid induction of Alzheimer Aβ amyloid formation by zinc. *Science* **265**: 1464–1467.

Bush AI, Pettingell WH Jr, Paradis MD, Tanzi RE. 1994b. Modulation of Aβ adhesiveness and secretase site cleavage by zinc. *J Biol Chem* **269**: 12152–12158.

Cacciatore F, Abete P, Ferrara N, Paolisso G, Amato L, Canonico S, Maggi S, Rengo F. 1997. The role of blood pressure in cognitive impairment in an elderly population. *J Hypertension* **15**: 135–142.

Cai X-D, Golde TE, Younkin SG. 1993. Release of excess amyloid β protein from a mutant amyloid β protein precursor. *Science* **259**: 514–516.

Calhoun ME, Widerhold KH, Abramowski D, Phinney AL, Probst A, Sturchler-Pierrat C, Staufenbiel M, Sommer B, Jucker M. 1998. Neuron loss in APP transgenic mice. *Nature* **395**: 755–756.

Callahan CM, Hall KS, Hui SL, Musick BS, Unverzagt FT, Hendrie HC. 1996. Relationship of age, education, and occupation with dementia among a community-based sample of African Americans. *Arch Neurol* **53**: 134–140.

Calza L, Giardino L, Aloe L. 1997. Thyroid hormone regulates NGF content and $p75^{LNGFR}$ expression in the basal forebrain of adult rats. *Exp Neurol* **143**: 196–206.

Campion D, Flaman JM, Brice A, Hannequin D, Dubois B, Martin C, Moreau V, Charbonnier F, Didier-Jean O, Tardieu S, Penet C, Puel M, Pasquier F, Ledoze F, Bellis G, Calenda A, Heilig R, Martinez M, Mallet J, Bellis M, Clerget-Darpoux F, Agid Y, Frebourg T. 1995. Mutations of the presenilin-I gene in families with early-onset Alzheimer's disease. *Hum Molec Genetics* **4**: 2373–2377.

Candy J, Oakley A, Klinowski J, Carpenter TA, Perry RH, Atack JR, Perry EK, Blessed G, Fairbairn A, Edwardson JA. 1986. Aluminosilicates and senile plaque formation in Alzheimer's disease. *Lancet* **1**: 354–357.

Canossa M, Griesbeck O, Berninger B, Campana G, Kolbeck R, Thoenen H. 1997. Neurotrophin release by neurotrophins: Implications for activity-dependent neuronal plasticity. *Proc Natl Acad Sci USA* **94**: 13279–13286.

Capell A, Saffrich R, Olivo JC, Meyn L, Walter J, Grunberg J, Mathews P, Nixon R, Dotti C, Haass C. 1997. Cellular expression and proteolytic processing of presenilin proteins is developmentally regulated during neuronal differentiation. *J Neurochem* **69**: 2432–2440.

Cardenas DD, McLean A, Farrell-Roberts L, Baker L, Brooke M, Haselkorn J. 1994. Oral physostigmine and impaired memory in adults with brain injury. *Brain Injury* **8**: 579–587.

Carlesimo GA, Sabbadini M, Loasses A, Caltagirone C. 1997. Forgetting from long-term memory in severe closed-head injury patients: Effect of retrieval conditions and semantic organization. *Cortex* **33**: 131–142.

Carmelli D, Swan GE, Reed T, Miller B, Wolf PA, Jarvik GP, Schellenberg GD. 1998. Midlife cardiovascular risk factors, ApoE, and cognitive decline in elderly male twins. *Neurology* **50**: 1580–1585.

Carmelli D, Swan GE, Reed T, Schellenberg GD, Christian JC. 1999. The effect of apolipoprotein E ε4 in the relationships of smoking and drinking to cognitive function. *Neuroepidmiology* **18**: 125–133.

Casalino E, Sblano C, Landriscina C. 1997. Enzyme activity alteration by cadmium administration to rats: the possibility of iron involvement in lipid peroxidation. *Arch Biochem Biophys* **346**: 171–179.

Casanova MF, Walker LC, Whitehouse PJ, Price DL. 1985. Abnormalities of the nucleus basalis in Down's syndrome. *Ann Neurol* **18**: 310–313.

Castelnau PA, Garrett RS, Palinski W, Witztum JL, Campbell IL, Powell HC. 1998. Abnormal iron deposition associated with lipid peroxidation in transgenic mice expressing interleukin-6 in the brain. *J Neuropathol Exp Neurol* **57**: 268–282.

Castilho RF, Kowaltowski AJ, Vercesi AE. 1988. 3,5,3′-triiodothyronine induces mitochondrial permeability transition mediated by reactive oxygen species and membrane thiol oxidation. *Arch Biochem Biophys* **354**: 151–157.

Ceccarelli D, Gallesi D, Giovannini F, Ferrali M, Masini A. 1995. Relationship between free iron level and rat liver mitochondrial dysfunction in experimental dietary iron overload. *Biochem Biophys Res Commun* **209**: 53–59.

Chafi AH, Hauw J-J, Rancurel G, Berry J-P, Galle C. 1991. Absence of aluminum in Alzheimer's disease brain tissue: electron microprobe and ion microprobe studies. *Neurosci Lett* **123**: 61–64.

Chancellor-Freeland C, Zhu GF, Kage R, Beller DI, Leeman SE, Black PH. 1995. Substance P and stress-induced changes in macrophages. *Ann NY Acad Sci* **771**: 472–484.

Chandra V, Pandav R. 1998. Gene-environment interaction in Alzheimer's disease: A potential role for cholesterol. *Neuroepidemiology* **17**: 225–232.

Chandra V, Ganguli M, Pandav R, Johnston J, Belle S, DeKosky ST. 1998. Prevalnece of Alzheimer's disease and other dementias in rural India: The Indo US study. *Neurology* **51**: 1000–1008.

Chapman PF, White GL, Jones MW, Cooper-Blacketer D, Marshall VJ, Irizarry M, Younkin L, Good MA, Bliss TVP, Hyman BT, Younkin SG, Hsssiao KK. 1999. Impaired synaptic plasticity and learning in aged amyloid precursor protein transfenic mice. *Nature Neurosci* **2**: 271–276.

Chartier-Harlin MC, Crawford F, Houlden H, Warren A, Hughes D, Fidani L, Goate A, Rossor M, Roques P, Hardy J, Mullan M. 1991. Early Alzheimer's disease caused by mutations at codon 717 of the beta-amyloid precursor protein gene. *Nature* **353**: 844–846.

Choi JH, Yu BP. 1995. Brain synaptosomal aging: free radicals and membrane fluidity. *Free Radic Biol Med* **18**: 133–139.

Ciallela JR, Yan HQ, Ma X, Marion DW, DeKosky ST, Dixon CE. 1998. Chronic overexpression of amyloid precursor protein (APP) after traumatic brain injury in rats. *Soc Neurosci Abstr* **24**: 725.

Citron M, Oltersdorf T, Haass C, McConlogue L, Hung

AY, Seubert P, Vigo-Pelfrey C, Lieberburg I, Selkoe DJ. 1992. Mutation of the β-amyloid precursor protein in familial Alzheimer's disease increases β-protein production. *Nature* **360**: 672–674.

Citron M, Vigo-Pelfrey C, Teplow DB, Miller C, Schenk D, Johnston J, Winblad B, Venizelos N, Lannfelt L, Selkoe DJ. 1994. Excessive productionof amyloid β-protein by peripheral cells of symptomatic and presymptomatic patients carrying the Swedish familial Alzheimer's disease mutation. *Proc Natl Acad Sci USA* **91**: 11993–11997.

Citron M, Westaway D, Xia WM, Carlson G, Diehl T, Levesque G, Johnson-Wood K, Lee M, Seubert P, Davis A, Kholodenko D, Motter R, Sherrington R, Perry B, Yao H, Strome R, Lieberburg I, Rommens J, Kim S, Schenk D, Fraser P, Hyslop PS, Selkoe DJ. 1997. Mutant presenilins of Alzheimer's disease increase production of 42-residue amyloid β-protein in both transfected cells and transgenic mice. *Nature Med* **3**: 67–72.

Cizza G, Brady LS, Calogero AE, Bagdy G, Lynn AB, Kling MA, Blackman MR, Chrousos GP, Gold PW. 1992. Central hypothyroidism is associated with advanced age in male Fischer 344 rats: *in vivo* and *in vitro* studies. *Endocrinology* **131**: 2672–2680.

Cizza G, Brady LS, Pacak K, Blackman MR, Gold PW, Chrousos GP. 1995. Stress-induced inhibition of the hypothalamic–pituitary–thyroid axis is attenuated in the aged Fischer 344/N male rat. *Neuroendocrinology* **62**: 506–513.

Clarfield AM. 1988. The reversible dementias: do they reverse? *Ann Int Med* **109**: 476–486.

Clarke R, Smith AD, Jobst KA, Refsum H, Sutton L, Ueland PM. 1998. Folate, vitamin B-12, and serum total homocysteine levels in confirmed Alzheimer's disease. *Arch Neurol* **55**: 1449–1455.

Claus JJ, Breteler MMB, Hasan D, Krenning EP, Bots ML, Grobbee DE, van Swieten JC, van Harskamp F, Hofman A. 1996. Vascular risk factors, atherosclerosis, cerebral white matter lesions and cerebral perfusion in a population-based study. *Eur J Nucl Med* **23**: 675–682.

Claus JJ, Breteler MMB, Hasan D, Krenning EP, Bots ML, Grobbee DE, van Swieten JC, van Harskamp F, Hofman A. 1998. Regional cerebral blood flow and cerebrovascular risk factors in the elderly population. *Neurobiol Aging* **19**: 57–64.

Claustrat B, Chazot G, Brun J, Jordan D, Sassolas G. 1984. A chronobiological study of melatonin and cortisol secretion in depressed subjects: plasma melatonin, a biochemical marker in major depression. *Biol Psychiat* **19**: 1215–1228.

Clemens JA, Stephenson DT. 1992. Implants containing beta-amyloid protein are not neurotoxic to young and old rat brain. *Neurobiol Aging* **13**: 581–586.

Cobb JL, Wolf PA, Au R, White R, D'Agostino RB. 1995. The effect of education on the incidence of dementia and Alzheimer's disease in the Framingham Study. *Neurology* **45**: 1707–1712.

Coffey CE, Saxton JA, Ratcliff G, Bryan RN, Lucke JF. 1999. Relation of education to brain size in normal aging — Implications for the reserve hypothesis. *Neurology* **53**: 189–196.

Cohen D, Eisdorfer C, Leverenz J. 1982. Alzheimer's disease and maternal age. *J Am Geriatr Soc* **30**: 656–659.

Combarros O, Leno C, Oterino A, Berciano J, Fernandez-Luna JL, Fernandez-Viadero C, Pena N, Miro J, Delgado M. 1998. Gender effect on apolipoprotein E ε4 allele-associated risk for sporadic Alzheimer's disease. *Acta Neurolog Scand* **97**: 68–71.

Combarros O, Escribano J, Sanchez-Velasco P, Leyva-Cobian F, Oterino A, Leno C, Berciano J. 1998b. Association of the HLA-A2 allele with an earlier age of onset of Alzheimer's disease. *Acta Neurolog Scand* **98**: 140–141.

Connor JR, Tucker P, Johnson M, Snyder B. 1993. Ceruloplasmin levels in the human superior temporal gyrus in aging and Alzheimer's disease. *Neurosci Lett* **159**: 88–90.

Connor TJ, Leonard BE. 1998. Depression, stress and immunological activation: the role of cytokines in depressive disorders. *Life Sci* **62**: 583–606.

Cook DG, Sung JC, Golde TE, Felsenstein KM, Wojczyk BS, Tanzi RE, Trojanowski JQ, Lee VMY, Doms RW. 1996. Expression and analysis of presenilin-1 in a human neuronal system: localization in cell bodies and dendrites. *Proc Natl Acad Sci USA* **93**: 9223–9228.

Cooper DS, Halpern R, Wood LC, Levin AA, Ridgway EC. 1984. L-thyroxine therapy in subclinical hypothyroidism. A double-blind, placebo-controlled trial. *Ann Intern Med* **101**: 18–24.

Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA. 1993. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* **261**: 921–923.

Corder EH, Jelic V, Basun H, Lannfelt L, Valind S, Winblad B, Nordberg A. 1997. No difference in cerebral glucose metabolism in patients with Alzheimer's disease and differing apolipoprotein E genotypes. *Arch Neurol* **54**: 273–277.

Corder EH, Robertson K, Lannfelt L, Bogdanovic N. Eggertsen G, Wilkins J, Hall C. 1998. HIV-infected subjects with the E4 allele for APOE have excess dementia and peripheral neuropathy. *Nature Med* **4**: 1182–1184.

Corkin S, Rosen TJ, Sullivan EV, Clegg RA. 1989. Penetrating head injury in young adulthood exacerbates cognitive decline in later years. *J Neurosci* **9**: 3876–3883.

Cornett CR, Markesbery WR, Ehmann WD. 1998. Imbalances of trace elements related to oxidative damage in Alzheimer's disease brain. *Neurotoxicology* **19**: 339–345.

Corrigan FM, Reynolds GP, Ward NI. 1993. Hip-

pocampal tin, aluminum and zinc in Alzheimer's disease. *Biometals* **6**: 149–154.
Costantini F, Pierdomenico SD, DeCesare D, De Remigis P, Bucciarelli T, Bittolo-Bon G, Cazzolato G, Nubile G, Guagnano MT, Sensi S, Cuccurullo F, Mezzetti A. 1998. Effect of thyroid function on LDL oxidation. *Arteriosclerosis Thrombosis Vascular Biol* **18**: 732–737.
Court JA, Perry EK. 1994. CNS nicotinic receptors. Possible therapeutic targets in neurodegenerative disorders. *CNS Drugs* **2**: 216–233.
Crapper DR, Krishnan SS, Dalton AJ. 1973. Brain aluminum distribution in Alzheimer's disease and experimental neurofibrillary degeneration. *Science* **180**: 511–513.
Crapper DR, Krishnan SS, Quittkat S. 1976. Aluminium, neurofibrillary degeneration and Alzheimer's disease. *Brain* **99**: 67–80.
Crawford F, Suo ZM, Fang CH, Mullan M. 1998a. Characteristics of the *in vitro* vasoactivity of β-amyloid peptides. *Exp Neurol* **150**: 159–168.
Crawford F, Soto C, Suo ZM, Fang CH, Parker T, Sawar A, Frangione B, Mullan M. 1998b. Alzheimer's β-amyloid vasoactivity: identification of a novel β-amyloid conformational intermediate. *FEBS Lett* **436**: 445–448.
Crawford JG. 1996. Alzheimer's disease risk factors as related to cerebral blood flow. *Med Hypotheses* **46**: 367–377.
Crawford JG. 1998. Alzheimer's disease risk factors as related to cerebral blood flow: additional evidence. *Med Hypotheses* **50**: 25–36.
Crews FT, Camacho A, Phillips MI. 1983. Cholinergic stimulation of hippocampal pyramidal cells is inhibited by increasing membrane cholesterol. *Brain Res* **261**: 155–158.
Cribbs DH, Chen LS, Cotman CW, LaFerla FM. 1996. Injury induces presenilin-1 gene expression in mouse brain. *Neuroreport* **7**: 1773–1776.
Cruts M, Van Broeckhoven C. 1998. Presenilin mutation in Alzheimer's disease. *Hum Mutat* **11**: 183–190.
Cruts M, van Duijn CM, Backhovens H, Van den Broeck M, Wehnert A, Serneels S, Sherrington R, Hutton M, Hardy J, St George-Hyslop PH, Hofman A, Van Broeckhoven C. 1998. Estimation of the genetic contribution of presenilin-1 and -2 mutations in a population-based study of presenile Alzheimer's disease. *Hum Molec Genetics* **7**: 43–51.
Cuajungco MP, Lees GJ. 1997. Zinc metabolism in the brain: relevance to human neurodegenerative disorders. *Neurobiol Dis* **6**: 137–169.
Culvenor JG, Maher F, Evin G, Malchiodi-Albedi F, Cappai R, Underwood JR, Davis JB, Karran EH, Roberts GW, Beyreuther K, Masters CL. 1997. Alzheimer's disease-associated presenilin-1 in neuronal cells: Evidence for localization to the endoplasmic reticulum-Golgi intermediate compartment. *J Neurosci Res* **49**: 719–731.
Cunningham CC, Sinthusek G, Spach PI, Leathers C. 1981. Effect of dietary ethanol and cholesterol on metabolic functions of hepatic mitochondria and microsomes from the monkey, *Macaca nemestrina*. *Alcohol Clin Exp Res* **5**: 410–416.
Curran M, Middleton D, Edwardson J, Perry R, McKeith I, Morris C, Neill D. 1997. HLA-DR antigens associated with major genetic risk for late-onset Alzheimer's disease. *Neuroreport* **8**: 1467–1469.
Czech C, Forstl H, Hentschel F, Monning U, Besthorn C, Geiger-Kabisch C, Sattel H, Masters C, Beyreuther K. 1994. Apolipoprotein E-4 gene dose in clinically diagnosed Alzheimer's disease: prevalence, plasma cholesterol levels and cerebrovascular change. *Eur Arch Psychiat Clin Neurosci* **243**: 291–292.
Dahabra S, Ashton CH, Bahrainian M, Britton PG, Ferrier IN, McAllister VA, Marsh VR, Moore PB. 1998. Structural and functional abnormalities in elderly patients clinically recovered from early- and late-onset depression. *Biol Psychiat* **44**: 34–46.
Darko DF, Lucas AH, Gillin JC, Risch SC, Golshan S, Hamburger RN, Silverman MB, Janowsky DS. 1988. Cellular immunity and the hypothalamic-pituitary axis in major affective disorder: a preliminary study. *Psychiat Res* **25**: 1–9.
Davis DG, Schmitt FA, Wekstein DR, Markesbery WR. 1999. Alzheimer neuropathologic alterations in aged cognitively normal subjects. *J Neuropathol Exp Neurol* **58**: 376–388.
Cavis RE, Miller S, Herrnstadt C, Ghosh SS, Fahy E, Shinobu LA, Galasko D, Thal LJ, Beal MF, Howell N, Parker WD. 1997. Mutations in mitochondrial cytochrome c oxidase genes segregate with late-onset Alzheimer's disease. *Proc Nat Acad Sci USA* **94**: 4526–4531.
DeAngelis MM, Hayes RL, Lyeth BG. 1994. Traumatic brain injury causes a decrease in M2 muscarinic cholinergic receptor binding in rat brain. *Brain Res* **653**: 39–44.
Decker MW, Majchrzak MJ, Anderson DJ. 1992. Effects of nicotine on spatial memory deficits in rats with septal lesions. *Brain Res* **572**: 281–285.
Dedman DJ, Treffry A, Candy JM, Taylor GA, Morris CM, Bloxham CA, Perry RH, Edwardson JA, Harrison PM. 1992. Iron and aluminium in relation to brain ferritin in normal individuals and Alzheimer's disease and chronic renal-dialysis patients. *Biochem J* **287**: 509–514
Deibel MA, Ehmann WD, Markesbery WR. 1996. Copper, iron, and zinc imbalances in severely degenerated brain regions in Alzheimer's disease: possible relation to oxidative stress. *J Neurol Sci* **143**: 137–142.
De Jong GI, De Vos RAI, Jansen Steur ENH, Luiten PGM. 1997. Cerebrovascular hypoperfusion: A risk factor for Alzheimer's disease? Animal model and postmortem human studies. *Ann NY Acad Sci* **826**: 56–74.
de la Monte SM, Hedley-Whyte ET. 1990. Small cerebral hemispheres in adults with Down's syndrome: con-

tributions of developmental arrest and lesions of Alzheimer's disease. *J Neuropathol Exp Neurol* **49**: 509–520.

de la Torre JC. 1997a. Cerebromicrovascular pathology in Alzheimer's disease compared to normal aging. *Gerontology* **43**: 26–43.

de la Torre JC. 1997b. Hemodynamic consequences of deformed microvessels in the brain in Alzheimer's disease. *Ann NY Acad Sci* **826**: 75–91.

de la Torre JC. 1998. Regional cytochrome oxidase decline predicts neuronal atrophy after chronic brain hypoperfusion. *Neurobiol Aging* **10**(Suppl. 4): S263.

de la Torre JC. 1999. Critical threshold cerebral hypoperfusion causes Alzheimer's disease? *Acta Neuropathol* **98**: 1–8.

de la Torre JC, Cada A, Nelson N, Davis G, Sutherland RJ, Gonzalez-Lima F. 1997. Reduced cytochrome oxidase and memory dysfunction after chronic brain ischemia in aged rats. *Neurosci Lett* **223**: 165–168.

Del Bo R, Comi GP, Bresolin N, Castelli E, Conti E, Degiuli A, Ausenda CD, Scarlato G. 1997. The apolipoprotein E ε4 allele causes a faster decline of cognitive performances in Down's syndrome subjects. *J Neurol Sci* **145**: 87–91.

de Leeuw F-E, de Groot JC, Achten E, Heijboer R, Oudkerk M, van Gijn J, Hofman A, Breteler MMB. 1998. Duration of hypertension and cerebral white matter changes. The Rotterdam Scan Study. *Neurobiol Aging* **19**(Suppl. 4): S243.

DeMattos RB, Curtiss LK, Williams DL. 1998. A minimally lipidated form of cell-derived apolipoprotein E exhibits isoform-specific stimulation of neurite outgrowth in the absence of exogenous lipids or lipoproteins. *J Biol Chem* **273**: 4206–4212.

Dembri A, Belkhiria M, Michel O, Michel R. 1983. Effects of short- and long-term thyroidectomy on mitochondrial and nuclear activity in adult rat brain. *Mol Cell Endocrinol* **33**: 211–223.

Deng GM, Pike CJ, Cotman CW. 1996. Alzheimer-associated presenilin-2 confers increased sensitivity to apoptosis in PC12 cells. *FEBS Lett* **397**: 50–54.

Denisova NA, Strain JG, Joseph JA. 1997. Oxidant injury in PC12 cells — A possible model of calcium 'dysregulation' in aging. 2. Interactions with membrane lipids. *J Neurochem* **69**: 1259–1266.

Denisova NA, Erat SA, Kelly JF, Roth GS. 1998. Differential effect of aging on cholesterol modulation of carbachol-stimulated low-K_m GTPase in striatal synaptosomes. *Exp Gerontol* **33**: 249–265.

De Pedis G, Hedner K, Johansson BW, Stehen B. 1987. Cardiac arrhythmia in geriatric patients with organic dementia. *Compr Gerontol* **1**: 115–117.

Deplanque D, Lebert F, Jacob B, Henon H, Lavenu I, Leys D, Petit H, Pasquier F. 1998. Hyperlipemia and other vascular risk factors in patients with Alzheimer's disease and vascular dementia. The Lille Memory Clinic data base. *Neurobiol Aging* **19**(Suppl. 4): S245.

Desmond DW, Tatemichi TK, Paik M, Stern Y. 1993. Risk factors for cerebrovascular disease as correlates of cognitive function in a stroke-free cohort. *Arch Neruol* **50**: 162–166.

Desmond DW, Moroney JT, Bagiella E, Sano M, Stern Y. 1998. Dementia as a predictor of adverse outcomes following stroke: An evaluation of diagnostic methods. *Stroke* **29**: 69–74.

De Strooper B, Saftig P, Craessaerts K, Vanderstichele H, Guhde G, Annaert W, Von Figura K, Van Leuven F. 1998. Deficiency of presenilin-1 inhibits the normal cleavage of amyloid precursor protein. *Nature* **391**: 397–390.

Dettmers C, Hagendorff A, Luderitz B, Hartman A. 1997. Repetitive hypotensive episodes — their contribution to vascular cognitive impairment. *Nervenarzt* **68**: 625–632.

Devenny DA, Silverman WP, Hill AL, Jenkins E, Sersen EA, Wisniewski KE. 1996. Normal ageing in adults with Down's syndrome: a longitudinal study. *J Intellect Disabil Res* **40**: 208–221.

Dewji NN, Singer SJ. 1997. The seven-transmembrane spanning topography of the Alzheimer's disease-related presenilin proteins in the plasma membrane of cultured cells. *Proc Natl Acad Sci USA* **94**: 14025–14030.

Dewji NN, Singer SJ. 1998. Specific intercellular binding of the β-amyloid precursor protein to the presenilins induces intercellular signaling: Its significance for Alzheimer's disease. *Proc Natl Acad Sci USA* **95**: 15055–15060.

Diamond MC, Johnson RE, Protti AM, Ott C, Kajisa L. 1985. Plasticity in the 904-day-old male rat cerebral cortex. *Exp Neurol* **87**: 309–317.

Diaz JF, Merskey H, Hachinski VC, Lee DH, Boniferro M, Wong CJ, Mirsen TR, Fox H. 1991. Improved recognition of leukoaraiosis and cognitive impairment in Alzheimer's disease. *Arch Neurol* **48**: 1022–1025.

Dietrich WD, Alonso O, Busto R, Ginsberg MD. 1994. Widespread metabolic depression and reduced somatosensory circuit activation following traumatic brain injury in rats. *J Neurotrauma* **11**: 629–640.

Dikalov SI, Vitek MP, Maples KR, Mason RP. 1999. Amyloid β peptides do not form peptide-derived free radicals spontaneously, but can enhancemetal-catalyzed oxidation of hydroxylamines to nitroxides. *J Biol Chem* **274**: 9392–9399.

Dimitriadis GD, Leighton B, Parry-Billings M, West D, Newsholme EA. 1989. Effects of hypothyroidism on the sensitivity of glycolysis and glycogen synthesis to insulin in the soleus muscle of the rat. *Biochem J* **257**: 369–373.

Divakaran P, Venkataraman A. 1977. Effect of dietary fats on oxidative phosphorylation and fatty acid profile of rat liver mitochondria. *J Nutr* **107**: 1621–1631.

Dixon CE, Liu SJ, Jenkins LW, Bhattachargee M, Whitson JS, Yang KY, Hayes RL. 1995. Time course of increased vulnerability of cholinergic neurotransmission following traumatic brain injury in the rat. *Behav Brain Res* **70**: 125–131.

Dobbs CM, Vasquez M, Glaser R, Sheridan JF. 1993. Mechanisms of stress-induced modulation of viral pathogenesis and immunity. *J Neuroimmunol* **48**: 151–160.

Dowjat WK, Wisniewski T, Efthimiopoulos S, Wisniewski HM. 1999. Inhibition of neurite outgrowth by familial Alzheimer's disease-linked presenilin-1 mutations. *Neurosci Lett* **267**: 141–144.

Drinka PJ, Nolten WE. 1988. Subclinical hypothyroidism in the elderly: to treat or not to treat? *Am J Med Sci* **295**: 125–128.

Duara R, Lopez-Alberola RF, Barker WW, Loewenstein DA, Zatinsky M, Eisdorfer CE, Weinberg GB. 1993. A comparison of familial and sporadic Alzheimer's disease. *Neurology* **43**: 1377–1384.

Dubovsky SL. 1994. Editorial. Why don't we hear more about the calcium antagonists? *Biol Psychiat* **35**: 149–150.

Duff K, Eckman C, Zehr C, Yu X, Prada C-M, Perez-Tur J, Hutton M, Buee L, Harigaya Y, Yager D, Morgan D, Gordon MN, Holcomb L, Refolo L, Zenk B, Hardy J, Younkin S. 1996. Increased amyloid-β42(43) in brains of mice expressing mutant presenilin 1. *Nature* **383**: 710–713.

Ebly EM. Schaefer JP, Campbell NRC, Hogan DB. 1998. Folate status, vascular disease and cognition in elderly Canadians. *Age Ageing* **27**: 485–491.

Ebmeier KP, Glabus MF, Prentice N, Ryman A, Goodwin GM. 1998. A voxel-based analysis of cerebral perfusion in dementia and depression of old age. *Neuroimage* **7**: 199–208.

Echegoyen S, Oliva EB, Sepulveda J, Diaz-Zagoya JC, Espinos-Garcia MT, Pardo JP, Martinez F. 1993. Cholesterol increase in mitochondria: its effect on inner-membrane functions, submitochondrial localization and ultrastructural morphology. *Biochem J* **289**: 703–708.

Edland SD, Silverman JM, Peskind ER, Tsuang D, Wijsman E, Morris JC. 1996. Increased risk of dementia in mothers of Alzheimer's disease cases: evidence for maternal inheritance. *Neurology* **47**: 254–256.

Edwardson JA, Moore PB, Ferrier IN, Lilley JS, Newton GWA, Barker J, Templar J, Day JP. 1993. Effect of silicon on gastrointestinal absorption of aluminum. *Lancet* **342**: 211–212.

Egensperger R, Kosel S, Schnopp NM, Mehraein P, Graeber MB. 1997. Association of the mitochondrial tRNA(A4336G) mutation with Alzheimer's and Parkinson's diseases. *Neuropathol Appl Neurobiol* **23**: 315–321.

Egensperger R, Kosel S, von Eitzen U, Graeber MB. 1998. Microglial activation in Alzheimer's disease: Association with APOE genotype. *Brain Pathol* **8**: 439–447.

Eggleston DW, Nylander M. 1987. Correlation of dental amalgam with mercury in brain tissue. *J Prosthet Dent* **58**: 704–707.

Ehmann WD, Markesbery WR, Alauddin M, Hossain TIM, Brubaker EH. 1986. Brain trace elements in Alzheimer's disease. *Neurotoxicology* **7**: 197–206.

Einstein G, Bautista P, Patel V, Kenna M, Melone L, Fader R, Karson K, Saunders A, Hulette C, Roses A, Schmechel D. 1995. Distribution of apoE-immunoreactive neurons in control and AD brains. *Soc Neurosci Abstr* **21**: 1008.

Elenkov IJ, Webster EL, Torpy DJ, Chrousos GP. 1999. Stress, corticotropin-releasing hormone, glucocorticoids and the immune/inflammatory response: acute and chronic effects. *Ann NY Acad Sci* **876**: 1–11.

Elias MF, Wolf PA, D'Agostino RB, Cobb J, White LR. 1993. Untreated blood pressure level is inversely related to cognitive functioning: The Framingham Study. *Am J Epidemiol* **138**: 353–364.

Ellis RJ, Olichney JM, Thal LJ, Mirra SS, Morris JC, Beekly D, Heyman A. 1996. Cerebral amyloid angiopathy in the brains of patients with Alzheimer's disease: the CERAD expereince, part XV. *Neurology* **46**: 1592–1596.

Ely DL. 1995. Organization of cardiovascular and neurohumoral responses to stress. Implications for health and disease. *Ann NY Acad Sci* **771**: 594–608.

Emanuel I, Sever LE, Milham S, Thuline HC. 1972. Accelerated ageing in young mothers of children with Down's syndrome. *Lancet* **ii**: 361–363.

Endo Y, Nishmura JI, Kimura F. 1996. Impairment of maze learning in rats following long-term glucocorticoid treatments. *Neurosci Lett* **203**: 199–202.

Evans DA, Beckett LA, Albert MS, Hebert LE, Scherr PA, Funkenstein HH, Taylor JO. 1993. Level of education and change in cognitive function in a community population of older persons. *Ann Epidemiol* **3**: 71–77.

Evans DA, Hebert LE, Beckett LA, Scherr PA, Albert MS, Chown MJ, Pilgrim DM, Taylor JO. 1997. Education and other measures of socioeconomic status and risk of incident Alzheimer's disease in a defined population of older persons. *Arch Neurol* **54**: 1399–1405.

Evans DAP, Burbach JPH, Van Leeuwen FW. 1995. Somatic mutations in the brain: relationship to aging? *Mutat Res* **338**: 173–182.

Evenhuis HM. 1997. The natural history of dementia in ageing people with intellectual disability. *J Intellect Disability Res* **41**: 92–96.

Ewins DL, Rossor MN, Butler J, Roques PK, Mullan MJ, McGregor AM. 1991. Association between autoimmune thyroid disease and familial Alzheimer's disease. *Clin Endocrinol* **35**: 93–96.

Faden AI, Demediuk P, Panter SS, Vink R. 1989. The role of excitatory amino acids and NMDA receptors in traumatic brain injury. *Science* **244**: 798–800.

Fagan AM, Holtzman DM, Sun Y, Wu S, Mathur T, Getz GS, Reardon CA, Lukens J, Shah JA, LaDu MJ. 1998. Lipoprotein secretion by primary astrocytes from wild type, APOE null and human APOE transgenic mice. *Soc Neurosci Abstr* **24**: 1712.

Faist E, Schinkel C, Zimmer S. 1996. Update on the mechanisms of immune suppression of injury and immune modulation. *World J Surg* **20**: 454–459.

Farkas E, de Jong GI, de Vos RAI, Jansen Steur ENH, Luiten PGM. 1999. Cerebral microvascular breakdown in Alzheimer's disease and in experimental cerebral hypoperfusion. In *Alzheimer's Disease and Related Disorders. Etiology, Pathogenesis and Therapetics*, Iqbal K, Swaab DF, Winblad B, Wisniewski HM (eds). John Wiley & Sons: Chichester; 165–170.

Farrer LA, Myers RH, Connor L, Cupples LA, Growdon JH. 1991. Segregation analysis reveals evidence of a major gene for Alzheimer's disease. *Am J Hum Genet* **48**: 1026–1033.

Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, Myers RH, Pericak-Vance MA, Risch N, van Duijn CM. 1997. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer's disease. A meta-analysis. APOE and Alzheimer's disease Meta Analysis Consortium. *JAMA* **278**: 1349–1356.

Felsenstein KM, Hunihan LW, Roberts SB. 1994. Altered cleavage and secretion of a recombinant β-APP bearing the Swedish familial Alzheimer's disease mutation. *Nature Genetics* **6**: 251–255.

Fenner ME, Hewitt KE, Torpy DM. 1987. Down's syndrome: intellectual and behavioural functioning during adulthood. *J Ment Defic Res* **31**: 241–249.

Fernandez V, Videla LA. 1993. Influence of hyperthyroidism on superoxide radical and hydrogen peroxide production by rat liver submitochondrial particles. *Free Radic Res Commun* **18**: 329–335.

Ferrer I, Gullotta F. 1990. Down's syndrome and Alzheimer's disease: dendritic spine counts in the hippocampus. *Acta Neuropathol (Berl)* **79**: 680–685.

Ferrini M, Piroli G, Frontera M, Falbo A, Lima A, De Nicola AF. 1999. Estrogens normalize the hypothalamic–pituitary–adrenal axis response to stress and increase glucocorticoid receptor immunoreactivity in hippocampus of aging male rats. *Neuroendocrinology* **69**: 129–137.

Filley CM, Cullum CM. 1997. Education and cognitive function in Alzheimer's disease. *Neuropsychiat Neuropsychol Behav Neurol* **10**: 48–51.

Fincham JE, Faber M, Weight MJ, Labadarios D, Taljaard JJ, Steytler JG, Jacobs P, Kritchevsky D. 1987. Diets realistic for westernized people significantly affect lipoproteins, calcium, zinc, vitamins C, E, B6 and haematology in vervet minkeys. *Atherosclerosis* **66**: 191–203.

Finkelstein Y, Koffler B, Rabey JM, Gilad GM. 1985. Dynamics of cholinergic synaptic mechanisms in rat hippocampus after stress. *Brain Res* **343**: 314–319.

Fioravanti M, Ferrario E, Massaia M, Cappa G, Rivolta G, Grossi E, Buckley AE. 1997. Low folate levels in the cognitive decline of elderly patients and the efficacy of folate as a treatment for improving memory deficits. *Arch Gerontol Geriatr* **26**: 1–13.

Flaten TP. 1990. Geographical associations between aluminium in drinking water and death rates with dementia (including Alzheimer's disease), Parkinson's disease, and amyotrophic lateral sclerosis in Norway. *Environ Geochem Hlth* **12**: 152–167.

Fleming LM, Weisgraber KH, Strittmatter WJ, Troncoso JC, Johnson GVW. 1996. Differential binding of apolipoprotein E isoforms to tau and other cytoskeletal proteins. *Exp Neurol* **138**: 252–260.

Focht SJ, Snyder BS, Beard JL, Van Gelder W, Williams LR, Connor JR. 1997. Regional distribution of iron, transferrin, ferritin, and oxidatively-modified proteins in young and aged Fischer 344 rat brains. *Neuroscience* **79**: 255–261.

Forbes WF, Agwani N. 1994. A suggested mechanism for aluminum biotoxicity. *J Theoret Biol* **171**: 207–214.

Forbes WF, Gentleman JF, Maxwell CJ. 1995. Concerning the role of aluminum in causing dementia. *Exp Gerontol* **30**: 23–32.

Foreman PJ, Taglialatela G, Angelucci L, Turner CP, Perz-Polo JR. 1993. Nerve growth factor and $p75^{NGFR}$ factor receptor mRNA change in rodent CNS following stress activation of the hypothalamopituitary-adrenocortical axis. *J Neurosci Res* **36**: 10–18.

Forette F, Seux ML, Staessen JA, Thijs L, Birkenhager WH, Babarskiene MR, Babeanu S, Bossini A, Gil-Extremera B, Girerd X, Laks T, Lilov E, Moisseyev V, Tuomilehto J, Vanhanen H, Webster J, Yodfat Y, Fagard R. 1998. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. *Lancet* **352**: 1347–1351.

Forfar JC, Wathen CG, Todd WT, Bell GM, Hannan WH, Muir AL, Toft AD. 1985. Left ventricular performance in subclinical hypothyroidism. *Q J Med* **57**: 857–865.

Forget H, Cohen H, Somma M, Lacroix A. 1996. Glucocorticoid effects in Cushing's syndrome approximate cognitive aging. *Brain Cognit* **32**: 269.

Fox PL, Mukhopadhyay C, Ehrenwald E. 1996. Structure, oxidant activity, and cardiovascular mechanisms of human ceruloplasmin. *Life Sci* **56**: 1749–1758.

Foy CJ, Passmore AP, Vahidassr MD, Young IS, Lawson JT. 1999. Plasma chain-breaking antioxidants in Alzheimer's disease, vascular dementia and Parkinson's disease. *QJM-Monthly J Assoc Physicians* **92**: 39–45.

Frackowiak J, Mazur-Kolecka B, Wisniewski HM, Potempska A, Carroll RT, Emmerling MR, Kim KS. 1995. Secretion and accumulation of Alzheimer's β-protein by cultured vascular smooth muscle cells from old and young dogs. *Brain Res* **676**: 225–230.

Franklyn JA, Daykin J, Betteridge J, Hughes EA, Holder R, Jones SR, Sheppard MC. 1993. Thyroxine replacement therapy and circulating lipid concentrations. *Clin Endocrinol (Oxf)* **38**: 453–459.

Fratiglioni L, Ahlbom A, Viitanen M, Winblad B. 1993. Risk factors for late-onset Alzheimer's disease: a popu-

lation-based, case-control study. *Ann Neurol* **33**: 258–266.

Fratiglioni L, Viitanen M, Aguero-Torres H, Backman L, Winblad B. 1998. Low education and AD: Effects on diagnostics rather than risk. *Neurobiol Aging* **19**(Suppl. 4): S214.

Frautschy SA, Yang FS, Irrizarry M, Hyman B, Saido TC, Hsiao K, Cole GM. 1998. Microglial response to amyloid plaques in APPsw transgenic mice. *Am J Pathol* **152**: 307–317.

Frecker MF. 1991. Dementia in Newfoundland: identification of a geographical isolate? *Epidemiol Commun Hth* **45**: 307–311.

Friedland RP, Smyth KA, Rowland DY, Esteban-Santillan C, Koss E, Cole R, Lerner AJ, Whitehouse PJ, Petot G, Debanne SM. 1997. Pre-morbid activities are reduced in patients with Alzheimer's disease as compared to age- and sex-matched controls: results of a case-control study. In *Alzheimer's Disease: Biology, Diagnosis and Therapeutics*, Iqbal K, Winblad B, Nishimura T, Takeda M, Wisniewski HM (eds). John Wiley: Chichester; 33–37.

Friedman G, Froom P, Sazbon L, Grinblatt I, Shochina M, Tsenter J, Babaey S, Ben Yehuda A, Groswasser Z. 1999. Apolipoprotein E-ε4 genotype predicts poor outcome in survivors of traumatic brtin injury. *Neurology* **52**: 244–248.

Frishman WH, Sokol S, Aronson MK, Wassertheil-Smoller S, Katzman R. 1998. Risk factors for cardiovascular and cerebrovascular diseases and dementia in the elderly. *Curr Problems Cardiol* **23**: 7–62.

Fujii K, Sadoshima S, Okada Y, Yao H, Kuwabara Y, Ichiya Y, Fujishima M. 1990. Cerebral blood flow and metabolism in normotensive and hypertensive patients with transient neurologic deficits. *Stroke* **21**: 283–290.

Fujimoto Y, Matsui M, Fujita T. 1982. The accumulation of ascorbic acid and iron in rat liver mitochondria after lipid peroxidation. *Jpn J Pharmacol* **32**: 397–399.

Fujishima M, Ibayashi S, Fujii K, Mori S. 1995. Cerebral blood flow and brain function in hypertension. *Hypertension Res* **18**: 111–117.

Fujishima M, Kiyohara Y, Yoshitake T. 1998. Prevalence, incidence and risk factors of dementia in a defined elderly population in Japan: The Hisayama Study. *Neurobiol Aging* **19**(Suppl. 4): S65.

Fukuda H, Kitani M. 1995. Differences between treated and untreated hypertensive subjects in the extent of periventricular hyperintensities observed on brain MRI. *Stroke* **26**: 1593–1597.

Furukawa JS, Guo Q, Schellenberg GD, Mattson MP. 1998. Presenilin-1 mutation alters NGF-induced neurite outgrowth, calcium homeostasis, and transcription factor (AP-1) activation in PC12 cells. *J Neurosci Res* **52**: 618–624.

Gale CR, Martyn CN, Cooper C. 1996. Cognitive impairment and mortality in a cohort of elderly people. *Br Med J* **312**: 608–611.

Games D, Adams D, Allesandrini R, Barbour R, Berthelette P, Blackwell C, Carr T, Clemens J, Donaldson T, Gillespie F, Guido T, Hagopian S, Johnson-Wood K, Khan K, Lee M, Leibowitz P, Lieberburg I, Little S, Masliah E, McConlogue L, Montoya-Zavala M, Mucke L, Paganini L, Penniman E, Power M, Schenk D, Seubert P, Snyder B, Soriano F, Tan H, Vitale J, Wadsworth S, Wolozin B, Zhao J. 1995. Alzheimer-type neuropathology in transgenic mice overexpressing V717F β-amyloid precursor protein. *Nature* **373**: 523–527.

Gandolfi L, Stella MP, Zambenedetti P, Zatta P. 1998. Aluminum alters intracellular calcium homeostasis *in vitro*. *Biochim Biophys Acta* **1406**: 315–320.

Ganguli M, Burmeister LA, Seaberg EC, Belle S, DeKosky ST. 1996. Association between dementia and elevated TSH — A community-based study. *Biol Psychiat* **40**: 714–725.

Gao S, Hendrie HC, Hall KS. 1998. The relationships betwen age, sex, and the incidence of dementia and Alzheimer's disease. A meta-analysis. *Arch Gen Psychiat* **55**: 809–815.

Gattu M, Pauly JR, Boss KL, Summers JB, Buccafusco JJ. 1997. Cognitive impairment in spontaneously hypertensive rats: role of central nicotinic receptors. I. *Brain Res* **771**: 89–103.

Gatz M, Pedersen NL, Berg S, Johansson B, Johansson K, Mortimer JA, Posner SF, Viitanen M, Winblad B, Ahlbom A. 1997. Heritability for Alzheimer's disease: the study of dementia in Swedish twins. *J Gerontol A Biol Sci Med Sci* **52**: M117–M125.

Geerlings MI, Schmand B, Jonker C, Lindeboom J, Bouter LM. 1999. Education and incident Alzheimer's disease: A biased association due to selective attrition and use of a two-step diagnostic procedure: *Int J Epidemiol* **28**: 492–497.

Genovesi G, Paolini P, Marcellini L, Vernillo E, Salvati G, Polidori G, Ricciardi D, de Nuccio I, Re M. 1996. Relationship between autoimmune thyroid disease and Alzheimer's disease. *Panminerva Med* **38**: 61–63.

Gentleman SM, Roberts GW. 1991. Risk factors in Alzheimer's disease. *Br Med J* **304**: 118–119.

Gentleman SM, Graham DI, Roberts GW. 1993. Molecular pathology of head trauma — altered β-APP metabolism and the aetiology of Alzheimer's disease. *Progr Brain Res* **96**: 237–246.

Gerlach M, Ben-Shachar D, Riederer P, Youdim MB. 1994. Altered brain metabolism of iron as a cause of neurodegenerative diseases? *J Neurochem* **63**: 793–807.

Ghebremedhin E, Schultz C, Braak E, Braak H. 1998. High frequency of apolipoprotein E ε4 allele in young individuals with very mild Alzheimer's disease-related neurofibrillary changes. *Exp Neurol* **153**: 152–155.

Ghetti B, Murrell J, Benson MD, Farlow MR. 1992. Spectrum of amyloid β-protein immunoreactivity in hereditary Alzheimer's disease with a guanine to thymine missense change at position 1924 of the APP gene. *Brain Res* **571**: 133–139.

Ghosh C, Dick RM, Ali SF. 1993. Iron/ascorbate-

induced lipid peroxidation changes membrane fluidity and muscarinic cholinergic receptor binding in rat frontal cortex. *Neurochem Int* **23**: 479–484.

Giambarella U, Yamatsuji T, Okamoto T, Matsui T, Ikezu T, Murayama Y, Levine MA, Katz A, Gautam N, Nishimoto I. 1997. G protein beta gamma complex-mediated apoptosis by familial Alzheimer's disease mutant of APP. *EMBO J* **16**: 4897–4907.

Giannakopoulos P, Bouras C, Kovari E, Shioi J, Tezapsidis N, Hof PR, Robakis NK. 1997. Presenilil-l-immunoreactive neurons are preserved in late-onset Alzheimer's disease. *Am J Pathol* **150**: 429–436.

Gibbs RB. 1998. Impairment of basal forebrain cholinergic neurons associated with aging and long-term loss of ovarian function. *Exp Neurol* **151**: 289–302.

Gibson GE, Zhang U, Toralbarza L, Szolosi S, Tofel-Grehl B. 1996. Calcium stores in cultured fibroblasts and their changes with Alzheimer's disease. *Biochim Biophys Acta* **1316**: 71–77.

Gibson GE, Vestling M, Zhang H, Szolosi S, Alkon D, Lannfelt L, Gandy S, Cowburn RF. 1997. Abnormalities in Alzheimer's disease fibroblasts bearing the $APP^{670/671}$ mutation. *Neurobiol Aging* **18**: 573–580.

Gibson GE, Zhang H, Sheu KFR, Bogdanovich N, Lindsay JG, Lannfelt L, Vestling M, Cowburn RF. 1998. α-ketoglutarate dehydrogenase in Alzheimer brains bearing the APP670/671 mutation. *Ann Neurol* **44**: 676–681.

Gilad GM. 1987. The stress-induced response of the septo-hippocampal cholinergic system. A vectorial outcome of psychoneuroendocrinological interactions. *Psychoneuroendocrinology* **12**: 167–184.

Gilad GM, Gilas VH. 1995. Strain, stress, neurodegeneration and longevity. *Mech Ageing* **78**: 75–83.

Gilad GM, Rabey JM, Tizabi Y, Gilad VH. 1987. Age-dependent loss and compensatory changes of septohippocampal cholinergic neurons in two rat strains differing in longevity and response to stress. *Brain Res* **436**: 311–322.

Gilad GM, Gilad VH, Wyatt RJ, Tizabi Y. 1990. Region-selective stress-induced increase of glutamate uptake and release in rat forebrain. *Brain Res* **525**: 335–338.

Giles RE, Blanc H, Cann HM, Wallace DC. 1980. Maternal inheritance of human mitochondrial DNA. *Proc Natl Acad Sci USA* **77**: 6715–6719.

Gimpl G, Burger K, Fahrenholz F. 1997. Cholesterol as modulator of receptor function. *Biochem* **36**: 10959–10974.

Ginsberg L, Atack JR, Rapoport SI, Gershfield NL. 1993. Regional specificity of membrane instability in Alzheimer's disease brain. *Brain Res* **615**: 355–357.

Giubilei F, D'Antona R, Antonini R, Lenzi GL, Ricci G, Fieschi C. 1990. Serum lipoprotein pattern variations in dementia and ischemic stroke. *Acta Neurol Scand* **81**: 84–86.

Gleason MM, Medow MS, Tulenko TN. 1991. Excess membrane cholesterol alters calcium movements, cytosolic calcium levels, and membrane fluidity in arterial smooth muscle cells. *Cir Res* **69**: 216–227.

Glenner GG, Wong CW. 1984. Alzheimer's disease: Initial report of the purification and characterization of a novel cerebrovascular amyloid protein. *Biochem Biophys Res Commun* **120**: 885–890.

Glick M, Michel AC, Dorn J, Horwitz M, Rosenthal T, Trevisan M. 1998. Dietary cardiovascular risk factors and serum cholesterol in an Old Order Mennonite community. *Am J Publ Hlth* **88**: 1202–1205.

Glushakova NE, Misiuk EM, Taranovich GL. 1976. The activity of the dehydrogenases of the tricarboxylic acid cycle and concentration of adenylic nucleotides in the brain and liver in experimental hypothyroidism. *Probl Endokrinol* **22**: 50–54.

Glynn RJ, Beckett LA, Hebert LE, Morris MC, Scherr PA, Evans DA. 1999. Current and remote blood pressure and cognitive decline. *J Am Med Assoc* **281**: 438–445.

Goate A, Chartier-Harlin MC, Mullan M, Brown J, Crawford F, Fiani L, Giuffra L, Haynes A, Irving N, James L, Mant R, Newton P, Rooke K, Roques P, Talbot C, Pericak-Vance M, Roses A, Williamson R, Rossor M, Owen M, Hardy J. 1991. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature* **349**: 704–706.

Godridge H, Reynolds GP, Czudek C, Calcutt NA, Benton M. 1987. Alzheimer-like neurotransmitter deficits in adult Down's syndrome brain tissue. *J Neurol Neurosurg Psychiat* **50**: 775–778.

Gold G, Giannakopoulos P, Bouras C. 1998. Reevaluating the role of vascular changes in the differential diagnosis of Alzheimer's disease and vascular dementia. *Eur Neurol* **40**: 121–129.

Goldsmith HS. 1997. Omental transposition to the brain for Alzheimer's disease. *Ann NY Acad Sci* **826**: 323–336.

Gomez-Isla T, Wasco W, Pettingell WP, Gurubhagavatula S, Schmidt SD, Jondro PD, McNamara M, Rodes LA, DiBlasi T, Growdon WB, Seubert P, Schenk D, Growdon JH, Hyman BT, Tanzi RE. 1997. A novel presentil-1 mutation: increased β-amyloid and neurofibrillary changes. *Ann Neurol* **41**: 809–813.

Gonzalez AM, Pazos A. 1992. Affinity changes in muscarinic acetylcholine receptors in the rat brain following acute immobilization stress: an autoradiographic study. *Eur J Pharmacol* **214**: 261–268.

Good PF, Perl DP, Bierer LM, Schmeidler J. 1992. Selective accumulation of aluminum and iron in the neurofibrillary tangles of Alzheimer's disease: a laser microprobe (LAMMA) study. *Ann Neurol* **31**: 286–292.

Goodman YD, Bruce AJ, Cheng B, Mattson MP. 1996. Estrogens attenuate and corticosterone exacerbates excitotoxicity, oxidative injury, and amyloid β-peptide toxicity in hippocampal neurons. *J Neurochem* **66**: 1836–1844.

Gordon I, Beneliyahu S, Rosenne E, Sehayek E, Michael-

son DM. 1996. Derangement in stress-response of apolipoprotein E-deficient mice. *Neurosci Lett* **206**: 212–214.

Gorman JM, Sullivan G, Hatterer J, Chen X, Herbert J. 1997. Transthyretin is reduced in CSF of depressed patients. *Soc Neurosci Abstr* **23**: 1683.

Gould E, Woolley C, McEwen BS. 1991. The hippocampal formation: morphological changes induced by thyroid, gonadal and adrenal hormones. *Psychoneuroendocrinology* **16**: 67–84.

Gouras GK, Relkin NR, Sweeney D, Munoz DG, Mackenzie IR, Gandy S. 1997. Increased apolipoprotein E epsilon 4 in epilepsy with senile plaques. *Ann Neurol* **41**: 402–404.

Govoni S, Bergamaschi S, Gasparini L, Quaglia C, Racchi M, Cattaneo E, Binetti G, Bianchetti A, Giovetti F, Battaini F, Trabucchi M. 1996. Fibroblasts of patients affected by Down's syndrome oversecrete amyloid precursor protein and are hyporesponsive to protein kinase C stimulation. *Neurology* **47**: 1069–1075.

Gozes I, Brenneman DE. 1996. Activity-dependent neurotrophic factor (ADNF): An extracellular neuroprotective chaperonin? *J Molec Neurosci* **7**: 235–244.

Graham DI, Gentleman SJ, Lynch A, Roberts GW. 1995. Distribution of β-amyloid protein in the brain following severe head injury. *Neuropathol Appl Neurobiol* **21**: 27–34.

Gray R, Rajan AS, Radcliffe KA, Yakehiro M, Dani JA. 1996. Hippocampal synaptic transmission enhnaced by low concentrations of nicotine. *Nature* **383**: 713–716.

Greenwald BS, Kramer-Ginsberg E, Krishnan KRR, Ashtari M, Auerbach C, Patel M. 1998. Neuroanatomic localization of magnetic resonance imaging signal hyperintensities in geriatric depression. *Stroke* **29**: 613–617.

Griffin WS, Stanley LC, Ling C, White L, MacLeod V, Perrot LJ, White CL III, Araoz C. 1989. Brain interleukin 1 and S-100 immunoreactivity are elevated in Down's syndrome and Alzheimer's disease. *Proc Natl Acad Sci USA* **86**: 7611–7615.

Griffin WST, Sheng JG, Gentleman SM, Graham DI, Mrak RE, Roberts GW. 1994 Microglial interleukin-1α expression in human head injury: correlations with neuronal and neuritic β-amyloid precursor protein expression. *Neurosci Lett* **176**: 133–136.

Grinna LS. 1977. Age related changes in the lipids of the microsomal and the mitochondrial membranes of rat liver and kidney. *Mech Ageing Dev* **6**: 197–205.

Grootendorst J, de Kloet ER, Dalm S, Mulder M, Oitzl MS. 1998. Improved spatial learning of apolipoprotein E knockout mice following repeated exposure to rats. *Soc Neurosci Abstr* **24**: 1711.

Gross H, Kling A, Henry G, Herndon C, Lavretsky H. 1996. Local cerebral glucose metabolism in patients with long-term behavioral and cognitive deficits following mild traumatic brain injury. *J Neuropsychiat Clin Neurosci* **8**: 324–334.

Grundke-Iqbal I, Fleming J, Tung YC, Lassmann H, Iqbal K, Joshi JG. 1990. Ferritin is a component of the neuritic (senile) plaque in Alzheimer dementia. *Acta Neuropathol* **81**: 105–110.

Guo Q, Christakos S, Robinson N, Mattson MP. 1998. Calbindin D28k blocks the proapoptotic actions of mutant presentilin 1: Reduced oxidative stress and preserved mitochondrial function. *Proc Natl Acid Sci USA* **95**: 3227–3232.

Guo ZC, Viitanen M, Fratiglioni L, Winblad B. 1996. Low blood pressure and dementia in elderly people: the Kungsholmen Project. *Br Med J* **312**: 805–808.

Guo Z, Viitanen M, Fratiglioni L, Winblad B. 1997. Blood pressure and dementia in the elderly: epidemiologic perspectives. *Biomed Pharmacother* **51**: 68–73.

Guo ZC, Fratiglioni L, Zhu L, Fastbom J, Winblad B, Viitanen M. 1999. Occurrence and progression of dementia in a community population aged 75 years and older. Relationship of antihypertensive medication use. *Arch Neurol* **56**: 991–996.

Gutteridge JM. 1978. The membrane effects of vitamin E, cholesterol and their acetates on peroxidative susceptibility. *Res Commun Chem Pathol Pharmacol* **22**: 563–572.

Gutteridge JM, Quinlan GJ, Clark I, Halliwell B. 1985. Aluminum salts accelerate peroxidation of membrane lipids stimulated by iron salts. *Biochim Biophys Acta* **835**: 441–447.

Haan MN, Shemanski L, Jagust WJ, Manolio TA, Kuller L. 1999. The role of APOE ε4 in modulating effects of other risk factors for cognitive decline in elderly persons. *J Am Med Assoc* **282**: 40–46.

Haass C, Hung AY, Selkoe DJ, Teplow DB. 1994. Mutations associated with a locus for familial Alzheimer's disease result in alternative processing of amyloid β-protein precursor. *J Biol Chem* **269**: 17741–17748.

Hahn LJ, Kloiber R, Leininger RW, Vimy MJ, Lorscheider FL. 1990. Whole-body imaging of the distribution of mercury released from dental fillings into monkey tissues. *FASEB J* **4**: 3256–3260.

Hall K, Gureje O, Gao S, Ogunniyi A, Hui SL, Baiyewu O, Unverzagt FW, Oluwole S, Hendrie HC. 1998. Risk factors and Alzheimer's disease: a comparative study of two communities. *Australian N Zealand J Psychiat* **32**: 698–706.

Halliwell B. 1984. Manganese ions, oxidation reactions and the superoxide radical. *Neurotoxicology* **5**: 113–117.

Halliwell B, Gutteridge JM. 1992. Biologically relevant metal ion-dependent hydroxyl radical generation. An update. *FEBS Lett* **307**: 108–112.

Hamblet NS, Castora FJ. 1997. Elevated levels of the Kearns-Sayre syndrome mitochondrial DA deletion in temporal cortex of Alzheimer's patients. *Mutation Res — Fundamental Molec Mech Mutagenesis* **379**: 253–262.

Hamm RJ, White-Gbadebo D, Lyeth BG, Jenkins LW,

Hayes RL. 1992. The effect of age on motor and cognitive deficits after traumatic brain injury. *Neurosurgery* **31**: 1072–1078.

Hammami M, Meunier S, Maume G, Gambert P, Maume BF. 1991. Effect of rat plasma high density lipoprotein with or without apolipoprotein E on the cholesterol uptake and on the induction of the corticosteroid biosynthetic pathway in newborn rat adrenocortical cell cultures. *Biochim Biophys Acta* **1094**: 153–160.

Hamman RF, Barancik JI, Lilienfeld AM. 1981. Patterns of mortality in the Old Order Amish. I. Background and major causes of death. *Am J Epidemiol* **114**: 845–861.

Haourigui M, Vallette G, Martin ME, Sumida C, Benassayag C, Nunez EA. 1994. *In vivo* effect of free fatty acids on the specific binding of glucocorticosteroids to corticosteroid binding globulin and liver receptors in immature rats. *Steroids* **59**: 46–54.

Hardy J. 1997. Amyloid, the presenilins and Alzheimer's disease. *Trends Neurosci* **20**: 154–159.

Harper SL. 1987. Effects of antihypertensive treatment on the cerebral microvasculature of spontaneously hypertensive rats. *Stroke* **18**: 450–456.

Hartmann H, Eckert A, Muller WE. 1994. Apolipoprotein E and cholesterol affect neuronal calcium signalling: the possible relationship to β-amyloid neurotoxicity. *Biochem Biophys Res Commun* **200**: 1185–1192.

Hartmann H, Busciglio J, Baumann KH, Staufenbiel M, Yankner BA. 1997. Developmental regulation of presentilin-1 processing in the brain suggests a role in neuronal differentiation. *J Biol Chem* **272**: 14505–14508.

Hartmann HA, Evenson MA. 1992. Deficiency of copper can cause neuronal degeneration. *Med Hypotheses* **38**: 75–85.

Hasenfratz M, Battig K. 1994. Pretask smoking and smoking during task: Effects on cognitive performance, puffing behaviour, physiological and subjective parameters. *Human Psychopharmacol* **9**: 181–189.

Hassing L, Wahlin A, Winblad B, Backman L. 1999. Further evidence on the effects of vitamin B-12 and folate levels on episodic memory functioning: A population-based study of healthy very old adults. *Biol Psychiat* **45**: 1472–1480.

Hatterer JA, Herbert J, Hidaka C, Roose SP, Gorman JM. 1993. CSF transthyretin in patients with depression. *Am J Psychiat* **150**: 813–815.

Havlik R, Plassman B, Gau B, Guralnik J, Helms M, Phillips C, Breitner JCS. 1998. Early-life trauma as possible predictor of late-life cognitive disability. *Neurobiol Aging* **19**(Suppl. 4): S140.

Hayes RL, Dixon CE. 1994. Neurochemical changes in mild head injury. *Seminars Neurol* **14**: 25–31.

Hazell AS, Todd KG, Butterworth RF. 1998. Mechanisms of neuronal cell death in Wernicke's encephalopathy. *Metab Brain Dis* **13**: 97–122.

Hegg CC, Miletic V. 1997. Chronic exposure to inorganic lead increases high-threshold voltage-gated calcium currents in rat pheochromocytoma (PC12) cells. *Brain Res* **772**: 63–70.

Heim C, Owens MJ, Plotsky PM, Nemeroff CB. 1997. Persistent changes in corticotropin-releasing factor systems due to early life stress: relationship to the pathophysiology of major depression and post-traumatic stress disorder. *Psychopharmacol Bull* **33**: 185–192.

Heininger K. 1999a. A unifying hypothesis of Alzheimer's disease. I. Ageing sets the stage. *Hum Psychopharmacol Clin Exp* **14**: 363–414.

Heininger K. 1999b. A unifying hypothesis of Alzheimer's disease. II. Pathophysiological processes. *Hum Psychopharmacol Clin Exp* **14**: 525–581.

Heininger K, Hindmarch I, deVry J. 1998. Psychotropic potential of calcium antagonists. In *Calcium Ion Modulators. The New Wave of Psychotropic Drugs*, Inoue K, Watanabe Y (eds). Harwood Academic Publishers: Amsterdam; 147–160.

Heinrichs SC. 1999. Stress-axis, coping and dementia: gene manipulation studies. *TiPS* **20**: 311–315.

Helkala EL, Koivisto K, Hanninen T, Vanhanen M, Kervinen K, Kuusisto J, Mykkanen L, Kesaniemi YA, Laakso M, Riekkinen P. 1995. The association of apolipoprotein E polymorphism with memory. A population-based study. *Neurosci Lett* **191**: 141–144.

Hellerstein MK. 1989. Aging, diet, and the acute-phase response to inflammation. *Ann NY Acad Sci* **561**: 178–195.

Helmer C, Damon D, Letenneur L, Dartigues JF. 1999. Marital status and risk of Alzheimer's disease: A French population-based cohort study. In *Alzheimer's Disease and Related Disorders*, *Etiology*, *Pathogenesis and Therapeutics*, Iqbal K, Swaab DF, Winblad B, Wisniewski HM (eds). John Wiley & Sons: Chichester; 25–31.

Henderson AS, Jorm AF, Korten AE, Creasey H, McCusker E, Broe GA, Longley W, Anthony JH. 1992. Environmental risk factors for Alzheimer's disease: their relationship to age of onset and to familial or sporadic types. *Psychol Med* **22**: 429–436.

Hendrie HC, Hall KS, Hui S, Unverzagt FW, Yu CE, Lahiri DK, Sahota A, Farlow M, Musick B, Class CA, Brashear A, Burdine VE, Osuntokun BO, Ogunniyi AO, Gureje O, Baiyewu O, Schellenberg GD. 1995a. Apolipoprotein E genotypes and Alzheimer's disease in a community study of elderly African Americans. *Ann Neurol* **37**: 118–120.

Hendrie HC, Osuntokun BO, Hall KS, Ogunniyi AO, Hui SL, Unverzagt FW, Gureje O, Rodenberg CA, Baiyewu O, Musick BS, Adeyinka A, Farlow MR, Oluwole SO, Class CA, Komolafe O, Brashear A, Burdine V. 1995b. Prevalence of Alzheimer's disease and dementia in two communities: Nigerian Africans and African Americans. *Am J Psychiat* **152**: 1485–1492.

Hershey LA, Hershey CO, Varnes AW, Wongmongkolrit T, Strain WH. 1984. Zinc content in CSF, brain and

other tissues in Alzheimer's disease and aging. In *The Neurobiology of Zinc*, *Part B: Deficiency*, *Toxicity and Pathology*, Frederickson CJ, Howell GA, Kasarskis EJ (eds). Alan R. Liss: New York; 325–334.

Heston LL, Mastri AR, Anderson VE, White J. 1981. Dementia of the Alzheimer type: clinical genetics, natural history and associated conditions. *Arch Gen Psychiat* **38**: 1085–1091.

Heyman A, Wilkinson WE, Hurwitz BJ, Schmechel D, Sigmon AH, Weinberg T, Helms MJ, Swift M. 1983. Alzheimer's disease: genetic aspects and associated disorders. *Ann Neurol* **14**: 507–515.

Heyman A, Wilkinson WE, Stafford JA, Helms MJ, Sigmon AH, Weinberg T. 1984. Alzheimer's disease: a study of epidemiological aspects. *Ann Neurol* **15**: 335–341.

Heyman A, Fillenbaum GG, Welsh-Bohmer KA, Gearing M, Mirra SS, Mohs RC, Peterson BL, Pieper CF. 1998. Cerebral infarcts in patients in autopsy-proven Alzheimer's disease. CERAD, part XVIII. *Neurology* **51**: 159–162.

Hickie I, Scott E, Mitchell P, Wilhelm K, Austin MP, Bennett B. 1995. Sucortical hyperintensities on magnetic resonance imaging: Clinical correlates and prognostic significance in patients with severe depression. *Biol Psychiat* **37**: 151–160.

Higuchi M, Arai H, Nakagawa T, Higuchi S, Muramatsu T, Matsushita S, Kosaka YI, Itoh M, Sasaki H. 1997. Regional cerebral glucose utilization is modulated by the dosage of apolipoprotein E type 4 allele and α1-antichymotrypsin type A allele in Alzheimer's disease. *Neuroreport* **8**: 2639–2643.

Hille B. 1994. Modulationof ion-channel function by G-protein-coupled receptors. *Trends Neurosci* **17**: 531–536.

Hillier V, Salib E. 1997. A case-control study of smoking and Alzheimer's disease. *Int J Geriatr Psychiat* **12**: 295–300.

Hirano M, Shtilbans A, Mayeux R, Davidson MM, DiMauro S, Knowles JA, Schon EA. 1997. Apparent mtDNA heteroplasmy in Alzheimer's disease patients and in normals due to PCR amplification of nucleus-embedded mtDNA pseudogenes. *Proc Natl Acad Sci USA* **94**: 14894–14899.

Hirono N, Mori E, Yasuda M, Ishii K, Ikejiri Y, Imamura T, Shimomura T, Hashimoto M, Yamashita H, Sasaki M. 1998. Lack of association of apolipoprotein E ε4 allele dose with cerebral glucose metabolism in Alzheimer's disease. *Alzheimer Dis Assoc Disord* **12**: 362–367.

Hock C, Drasch G, Golombowski S, Muller-Spahn F, Willershausen-Zonnchen B, Schwarz P, Hock U, Growdon JH, Nitsch RM. 1998. Increased blood mercury levels in patients with Alzheimer's disease. *J Neural Transm* **105**: 59–68.

Hofman A, Ott A, Breteler MM, Bots ML, Slooter AJ, van Harskamp F, van Duijn CN, Van Broeckhoven C, Grobbee DE. 1997. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. *Lancet* **349**: 151–154.

Hogan DB, Ebly EM, Rockwood K. 1997. Weight, blood pressure, osmolarity, and glucose levels across various stages of Alzheimer's disease and vascular dementia. *Dement Geriatr Cogn Disord* **8**: 147–151.

Holder J, Warren AC. 1998 Prevalence of Alzheimer's disease and apolipoprotein E allele frequencies in the Old Order Amish. *J Neuropsychiat Clin Neurosci* **10**: 100–102.

Holland AJ, Hon J, Huppert FA, Stevens F, Watson P. 1998. Population-based study of the prevalence and presentation of dementia in adults with Down's syndrome. *Br J Psychiat* **172**: 493–498.

Hollenbach E, Ackermann S, Hyman BT, Rebeck GW. 1998. Confirmation of an association between a polymorphism in exon 3 of the low-density lipoprotein receptor-related protein gene and Alzheimer's disease. *Neurology* **50**: 1905–1907.

Holmin S, Soderlund J, Biberfeld P, Mathiesen T. 1998. Intracerebral inflammation after human brain contusion. *Neurosurgery* **42**: 291–298.

Holsboer F. 1995. Neuroendocrinology of mood disorders. In *Psychopharmacology: The Fourth Generation of Progress*, Bloom FE, Kupfer DJ (eds). Raven Press: New York; 957–969.

Holtzman DM, Fagan AM. 1998. Potential role of apoE in structural plasticity in the nervous system. Implications for disorders of the central nervous system. *Trends Cardiovasc Med* **8**: 250–255.

Holtzman DM, Santucci D, Kilbridge J, Chuacouzens J, Fontana DJ, Daniels SE, Johnson RM, Chen K, Sun YL, Carlson E, Alleva E, Epstein CJ, Mobley WC. 1996. Developmental abnormalities and age-related neurodegeneration in a mouse model of Down's syndrome. *Proc Natl Acad Sci USA* **93**: 13333–13338.

Hong-Goka BC, Chang F-LF. 1997. The association between hysterectomy and Alzheimer's disease. *Soc Neurosci Abstr* **23**: 1368.

Hortnagl H, Berger ML, Havelec L, Hornykiewicz O. 1993. Role of glucocorticoids in the cholinergic degeneration in rat hippocampus induced by ethylcholine aziridinium (AF64A). *J Neurosci* **13**: 2939–2945.

Hossmann K-A. 1996. Periinfarct depolarizations. *Cerebrovasc Brain Metab Rev* **8**: 195–208.

Howland DS, Trusko SP, Savage MJ, Reaume AG, Lang DM, Hirsch JD, Maeda N, Siman R, Greenberg BD, Scott RM, Flood DG. 1998. Modulation of secreted β-amyloid precursor protein and amyloid β peptide in brain by cholesterol. *J Biol Chem* **273**: 16576–16582.

Hsia AY, Masliah E, McConlogue L, Yu GQ, Tatsuno G, Hu K, Kholodenko D, Malenka RC, Nicoll RA, Mucke L. 1999. Plaque-independent disruptuon of neural circuits in Alzheimer's disease mouse models. *Proc Natl Acad Sci USA* **96**: 3228–3233.

Hsiao K. 1998. Transgenic mice expressing Alzheimer amyloid precursor proteins. *Exp Gerontol* **33**: 883–889.

Hsiao K, Chapman P, Nilsen S, Eckman C, Harigaya Y, Younkin S, Yang FS, Cole G. 1996. Correlative memory deficits, Aβ elevation, and amyloid plaques in transgenic mice. *Science* **274**: 99–102.

Hsu M, Sik A, Gallyas F, Horvath Z, Buzsaki G. 1994. Short-term and long-term changes in the postischemic hippocampus. *Ann NY Acad Sci* **743**: 121–140.

Huang DY, Goedert M, Jakes R, Weisgraber KH, Garner CC, Saunders AM, Pericak-Vance MA, Schmechel DE, Roses AD, Strittmatter WJ. 1994. Isoform-specific interactions of apolipoprotein E with the microtubule-associated protein MAP2c: implications for Alzheimer's disease. *Neurosci Lett* **182**: 55–58.

Huertas JR, Battino M, Barzanti V, Maranesi M, Parenti-Castelli G, Littarru GP, Turchetto E, Mataix FJ, Lenaz G. 1992. Mitochondrial and microsomal cholesterol mobilization after oxidative stress induced by adriamycin in rats fed with dietary olive and corn oil. *Life Sci* **50**: 2111–2118.

Huijbregts PPCW, Feskens EJM, Rasanen L, Fidanza F, Alberti-Fidanza A, Nissinen A, Giampaoli S, Kromhout D. 1998. Dietary patterns and cognitive function in elderly men in Finland, Italy and the Netherlands. *Eur J Clin Nutrit* **52**: 826–831.

Huitron-Resendiz S, Giacchino JL, Henriksen SJ. 1997. Nicotinic effects on excitatory neuronal activity in the prefrontal cortex. *Soc Neurosci Abstr* **23**: 257.

Hulette C, Nochlin D, McKeel D, Morris JC, Mirra SS, Sumi SM, Heyman A. 1997. Clinical-neuropathologic findings in multi-infarct dementia: A report of six autopsied cases. *Neurology* **48**: 668–672.

Hussain S, Rodgers DA, Duhart HM, Ali SF. 1997. Mercuric chloride-induced reactive oxygen species and its effects on antioxidant enzymes in different regions of rat brain. *J Environ Sci Hlth* **B32**: 395–409.

Hutchin T, Cortopassi G. 1995. A mitochondrial DNA clone is associated with increased risk for Alzheimer's disease. *Proc Natl Acad Sci USA* **92**: 6892–6895.

Hutchin TP, Heath PR, Pearson RC, Sinclair AJ. 1997. Mitochondrial DNA mutations in Alzheimer's disease. *Biochem Biophys Res Commun* **241**: 221–225.

Hyman BT, West HL, Rebeck GW, Lai F, Mann DMA. 1995. Neuropathological changes in Down's syndrome hippocampal formation: Effect of age and apolipoprotein E genotype. *Arch Neurol* **52**: 373–378.

Hyman BT, Gomez-Isla T, West H, Briggs M, Chung H, Growdon JH, Rebeck GW. 1996. Clinical and neuropathological correlates of apolipoprotein E genotype in Alzheimer's disease. Window on molecular epidemiology. *Ann NY Acad Sci* **777**: 158–165.

Igbavboa U, Avdulov NA, Schroeder F, Wood WG. 1996. Increasing age alters transbilayer fluidity and cholesterol asymmetry in synaptic plasma membranes of mice. *J Neurochem* **66**: 1717–1725.

Igbavboa U, Avdulov NA, Chochina SV, Wood WG. 1997. Transbilayer distribution of cholesterol is modified in brain synaptic plasma membranes of knockout mice deficient in low-density lipoprotein receptor, apolipoprotein E, or both proteins. *J Neurochem* **69**: 1661–1667.

Ikeda K, Urakami K, Isoe K, Nakashima K, Ohno K. 1998. High concentrations of PS-1 mRNA in skin fibroblasts of patients with Down's syndrome. *J Neurol Neurosurg Psychiat* **64**: 690–691.

Imberti R, Vairetti M, Richelmi P, Preseglio I, Bellomo G. 1994. Thyroxine pretreatment and halothane administration alter Ca^{2+} transport and transmembrane potential in rat liver mitochondria. An additional mechanism for halothane-induced liver damage in the hyperthyroid rat model. *Arch Toxicol* **68**: 103–109.

Iriuchijima T, Michimata T, Mizuma H, Murakami M, Yamada M, Mori M. 1991. Hypothyroidism inhibits the formation of inositol phosphate in response to carbachol in the striatum of adult rat. *Res Commun Chem Pathol Pharmacol* **73**: 173–180.

Irwin M. 1995. Psychoneuroimmunology of depression. In *Psychopharmacology: The Fourth Generation of Progress*, Bloom FE, Kupfer DJ (eds). Raven Press: New York; 983–998.

Ito E, Oka K, Etcheberrigaray R, Nelson TJ, McPhie DL, Tofel-Grehl B, Gibson GE, Alkon DL. 1994. Internal Ca^{2+} mobilization is altered in fibroblasts from patients with Alzheimer's disease. *Proc Natl Acad Sci USA* **91**: 534–538.

Itzhaki RF, Lin WR, Shang DH, Wilcock GK, Faragher B, Jamieson GA. 1997. Herpes simplex virus type 1 in brain and risk of Alzheimer's disease. *Lancet* **349**: 241–244.

Iwatsubo T, Mann DMA, Odaka A, Suzuki N, Ihara Y. 1995. Amyloid-β protein (Aβ) deposition: Aβ-42(43) precedes Aβ-40 in Down's syndrome. *Ann Neurol* **37**: 294–299.

Jacobs RW, Duong T, Jones RE, Trapp GA, Scheibel AB. 1989. A reexamination of aluminum in Alzheimer's disease: analysis by energy dispersive x-ray microprobe and flameless atomic absorption spectrophotometry. *Can J Neurol Sci* **16**: 498–503.

Jacobsson-Borin A, Aberg F, Dallner G. 1994. Lipid peroxidation of microsomal and mitochondrial membranes extracted with n-pentane and reconstituted with ubiquinol, dolichol and cholesterol. *Biochim Biophys Acta* **1213**: 159–166.

Jacoby RJ, Dolan RJ, Levy R, Baldy R. 1983. Quantiative computed tomography in elderly depressed patients. *Br J Psychiat* **143**: 124–127.

Jacqmin H, Commenges D, Letenneur L, Barberger-Gateau P, Dartigues JF. 1994. Components of drinking water and risk of cognitive impairment in the elderly. *Am J Epidemiol* **139**: 48–57.

Jain VK. 1972. A psychiatric study of hypothyroidism. *Psychiatr Clin* **5**: 121–130.

Jama JW, Launer LJ, Witteman JCM, den Breeijen JH, Breteler MMB, Grobbee DE, Hofman A. 1996. Dietary antioxidants and cognitive function in a population-based sample of older persons. The Rotterdam study. *Am J Epidemiol* **144**: 275–280.

Jarvik GP, Wijsman EM, Kukull WA, Schellenberg GD, Yu C, Larson EB. 1995. Interactions of apolipoprotein E genotype, total cholesterol level, age, and sex in prediction of Alzheimer's disease: a case-control study. *Neurology* **45**: 1092–1096.

Jefferies WA, Food MR, Gabathuler R, Rothenberger S, Yamada T, Yasuhara O, McGeer PL. 1996. Reactive microglia specifically associated with amyloid plaques in Alzheimer's disease brain tissue express melanotransferrin. *Brain Res* **712**: 122–126.

Jellinger K, Paulus W, Grundke-Iqbal I, Riederer P, Youdim MB. 1990. Brain iron and ferritin in Parkinson's and Alzheimer's diseases. *J Neural Transm Park Dis Dement Sect* **2**: 327–340.

Jenkins LW, Moszynski K, Lyeth BG, Lewelt W, Dewitt DS, Allen A, Dixon CE, Povlishock JT, Majewski TJ, Clifton GL, Young HF, Becker DP, Hayer RL. 1989. Increased vulnerability of the mildly traumatized rat brain to cerebral ischemia: the use of controlled secondary ischemia as a research tool to identify common or different mechanisms contributing to mechanical and ischemic brain injury. *Brain Res* **477**: 211–224.

Johnson CC, Rybicki BA, Brown G, D'Hondt E, Herpolsheimer B, Roth D, Jackson CE. 1997. Cognitive impairment in the Amish: A four county survey. *Int J Epidemiol* **26**: 387–394.

Johnson K, Lopera F, Jones K, Becker A, Sperling R, Londono J, Siergert I, Arcos M, Moreno S, Madrigal L, Ossa J, Pineda N, Ardila A, Roselli M, Kosik KS, Rios A. 1998. Presenilin-1-associated abnormalities in regional cerebral perfusion. *Neurobiol Aging* **19**(Suppl. 4): S83.

Johnson-Wood K, Lee M, Motter R, Hu K, Gordon G, Barbour R, Khan K, Gordon M, Tan H, Games D, Lieberburg I, Schenk D, Seubert P, McConlogue L. 1997. Amyloid precursor protein processing and Aβ42 deposition in a transgenic mouse model of Alzheimer's disease. *Proc Natl Acad Sci USA* **94**: 1550–1555.

Jones GM, Sahakian BJ, Levy R, Warburton DM, Gray JA. 1992. Effects of acute subcutaneous nicotine on attention, information processing and short-term memory in Alzheimer's disease. *Psychopharmacology* **108**: 485–494.

Jones K, Johnson KA, Becker JA, Spiers PA, Albert MS, Holman BL. 1998. Use of singular value decomposition to characterize age and gender differences in SPECT cerebral perfusion. *J Nucl Med* **39**: 965–973.

Jonker C, Schmand B, Lindeboom J, Havekes LM, Launer LJ. 1998. Association between apolipoprotein E ε4 in the rate of cognitive decline in community-dwelling elderly individuals with and without dementia. *Arch Neurol* **55**: 1065–1069.

Jordan BD, Relkin NR, Ravdin LD, Jacobs AR, Bennett A, Gandy S. 1997. Apolipoprotein E epsilon4 associated with chronic traumatic brain injury in boxing. *JAMA* **278**: 136–140.

Jordan J, Galindo MF, Miller RJ, Reardon CA, Getz GS, LaDu MJ. 1998. Isoform-specific effect of apolipoprotein E on cell survival and β-amyloid-induced toxicity in rat hippocampal pyramidal neuronal cultures. *J Neurosci* **18**: 195–204.

Jøgensen OS, Brooksbank BW, Balas R. 1990. Neuronal plasticity and astrocytic reaction in Down's syndrome and Alzheimer's disease. *J Neurol Sci* **98**: 63–79.

Jørgensen OS, Mogensen HS. 1997. Enhanced synaptic remodelling in Alzheimer's disease is not dependent upon the APOE genotype. In *Research Advances in Alzheimer's Disease and Related Disorders*, Iqbal K, Mortimer JA, Winblad B, Wisniewski HM (eds), John Wiley: Chichester; 390–394.

Jorm AF, van Duijn CM. Chandra V, Fratiglioni L, Graves AB, Heyman A, Kokmen E, Kondo K, Mortimer JA, Rocca WA, Shalat SL, Soininen H, Hofman A. 1991. Psychiatric history and related exposures as risk factors for Alzheimer's disease: a collaborative re-analysis of case-control studies. EURODEM Risk Factors Research Group. *Int J Epidemiol* **20**(Suppl. 2): S43–S47.

Jorm AF, Rodters B, Henderson AS, Korten AE, Jacomb PA, Christensen H, Mackinnon A. 1998. Ocupation type as a predictor of cognitive decline and dementia in old age. *Age Ageing* **27**: 477–483.

Joseph JA, Villalobos-Molinas R, Denisova NA, Erat S, Strain J. 1997. Cholesterol: a two-edged sword in brain aging. *Free Radic Biol Med* **22**: 455–462.

Jovanovic SV, Clements D, MacLeod K. 1998. Biomarkers of oxidative stress are significantly elevated in Down's syndrome. *Free Radic Biol Med* **25**: 1044–1048.

Joya-Pardo CJ, Londono, Pardo CA. 1991. Risk factors in clinically diagnosed Alzheimer's disease: A case-control study in Colombia (South America). In *Alzheimer's Disease: Basic Mechanisms*, *Diagnosis and Therapeutic Strategies*, Iqbal K, McLachlan DRC, Winblad B, Wisniewski HM (eds). John Wiley: Chichester; 363–368.

Kala SV, Hasinoff BB, Richardson JS. 1996. Brain samples from Alzheimer's patients have elevated levels of loosely bound iron. *Int J Neurosci* **86**: 263–269.

Kalaria RN. 1996. Cerebral vessels in ageing and Alzheimer's disease. *Pharmacol Ther* **72**: 193–214.

Kalaria RN. 1997. Cerebrovascular degeneration is related to amyloid-β protein deposition in Alzheimer's disease. *Ann NY Acad Sci* **826**: 263–271.

Kalaria RN, Cohen DL, Greenberg BD, Savage MJ, Bogdanovic NE, Winblad B, Lannfelt L, Adem A. 1996. Abundance of the longer Aβ(42) in neocortical and cerebrovascular amyloid β deposits in Swedish familial Alzheimer's disease and Down's syndrome. *Neuroreport* **7**: 1377–1381.

Kalaria RN, Ogeng'O JA, Patel NB, Sayi JG, Kitinya JN, Chande HM, Matuja WB, Mtui EP, Kimani JK, Premkumar DR, Koss E, Gatere S, Friedland RP. 1997. Evaluation of risk factors for Alzheimer's disease in elderly east Africans. *Brain Res Bull* **44**: 573–577.

Kalmijn S, Launer SJ, Ott A, Witteman JCM, Hofman

A, Breteler MMB. 1997. Dietary fat intake and the risk of incident dementia in the Rotterdam Study. *Ann Neurol* **42**: 776–782.

Kamboh MI, Evans RW, Aston CE. 1995. Genetic effect of apolipoprotein (A) and apolipoprotein E polymorphisms on plasama quantitative risk factors for coronary heart disease in American black women. *Atherosclerosis* **117**: 73–81.

Kanayama G, Takeda M, Niigawa H, Ikura Y, Tamii H, Taniguchi N, Kudo T, Miyamae Y, Morihara T, Nishimura T. 1996. The effects of repetitive mild brain injury on cotyskeletal protein and behavior. *Meth Find Exp Clin Pharmacol* **18**: 105–115.

Kaneko Y, Tsukamoto A. 1994. Thapsigargin-induced persistent intracellular calcium pool depletion and apoptosis in human hepatoma cells. *Cancer Lett* **97**: 147–155.

Kang DE, Saitoh T, Chen X, Xia Y, Masliah E, Hansen LA, Thomas RG, Thal LJ, Katzman R. 1997. Genetic association of the low-density lipoprotein receptor-related protein gene (LRP), an apolipoprotein E receptor, with late-onset Alzheimer's disease. *Neurology* **49**: 56–61.

Kanno J, Wakikawa A, Utsuyama M, Hirokawa K. 1997. Effect of restraint stress on immune system and experimental B16 melanoma metastasis in aged mice. *Mech Ageing Devel* **93**: 107–177.

Katzman R, Kawas C. 1994. The epidemiology of dementia and Alzheimer's disease. In *Alzheimer's Disease*, Terry RD, Katzman R, Bick KL (eds). Raven Press: New York; 105–122.

Katzman R, Terry R, DeTeresa R, Brown T, Davies P, Fuld P, Renbing X, Peck A. 1988. Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques. *Ann Neurol* **23**: 138–144.

Katzman R, Zhang MY, Chen PJ, Gu N, Jiang S, Saitoh T, Chen X, Klauber M, Thomas RG, Liu WT, Tu ESH. 1997. Effects of apolipoprotein E on dementia and aging in the Shanghai Survey of Dementia. *Neurology* **49**: 779–785.

Kaufer D, Friedman A, Seidman S, Soreq H. 1998a. Acute stress facilitates long-lasting changes in cholinergic gene expression. *Nature* **393**: 373–377.

Kaufer D, Friedman A, Pavlovsky L, Soreq H. 1998b. Stress-induced transcriptional modulation elicits weeks-long changes in cholinergic transmission. *Soc Neurosci Abstr* **24**: 1434.

Kawamata T, Tooyama I, Yamada T, Walker DG, McGeer PL. 1993. Lactotransferrin immunocytochemistry in Alzheimer and normal human brain. *Am J Pathol* **142**: 1574–1585.

Kay T, Newman B, Cavallo M, Resnick M. 1992. Neuropsychological diagnoses, disentangling multiple determinants of functional disability after mild traumatic brain injury. *Physical Med Rehab State Art Rev* **6**: 109–125.

Keenan PA, Jacobson MW, Soleymani RM, Mayes MD, Stress ME, Yaldoo DT. 1996. The effect on memory of chronic prednisone treatment in patients with systemic disease. *Neurology* **47**: 1396–1402.

Keenan PA, Kuhn TW. 1999. Do glucocorticoids have adverse effects on brain function? *CNS Drugs* **11**: 245–251.

Kellner CH, Rubinow DR, Gold PW, Post RM. 1983. Relationship of cortisol hypersecretion to brain CT scan alterations in depressed patients. *Psychiat Res* **8**: 191–197.

Kellner CH, Rubinow DR, Post RM. 1986. Cerebral ventricular size and cognitive impairment in depression. *J Affect Disord* **10**: 215–219.

Kellner M, Yassouridis A, Manz B, Steiger A, Holsboer F, Wiedemann K. 1997. Corticotropin-releasing hormone inhibits melatonin secretion in healthy volunteers — A potential link to low-melatonin syndrome in depression? *Neuroendocrinology* **65**: 284–290.

Kelly JF, Jospeh JA, Denisova NA, Erat S, Mason RP, Roth GS. 1995. Dissociation of the striatal GTPase and dopamine release responses to muscarinic cholinergic agonists in F344 rats: influence of age and dietary manipulation. *J Neurochem* **64**: 2755–2764.

Kelly KS, Hayslip B, Servaty HL. 1996 Psychoneuroendocrinological indicators of stress and intellectual performance among older adults: An exploratory study. *Exp Aging Res* **22**: 393–401.

Kempermann G, Kuhn HG, Gage FH. 1998. Experience-induced neurogenesis in the senescent dentate gyrus. *J Neurosci* **18**: 3206–3212.

Kannard ML, Feldman H, Yamada T, Jefferies WA. 1996. Serum levels of the iron binding protein p97 are elevated in Alzheimer's disease. *Nat Med* **2**: 1230–1235.

Kennedy AM, Rossor MN, Frackowiak RS. 1995. Positron emission tomography in familial Alzheimer's disease. *Alzheimer Dis Assoc Disord* **9**: 17–20.

Kennedy SH, Garfinkel PE, Parienti V, Costa D, Brown GM. 1989. Changes in melatonin levels but not cortisol levels are associated with depression in patients with eating disorders. *Arch Gen Psychiat* **46**: 73–78.

Kerr D, Campbell L, Hao S, Landfield P. 1989. Corticosteroid modulation of hippocampal potentials: Increased effect with aging. *Science* **245**: 1505–1509.

Kessler AR, Kessler B, Yehuda S. 1985. Changes in the cholesterol level, cholesterol-to-phospholipid mole ratio, and membrane lipid microviscosity in rat brain induced by age and a plant oil mixture. *Biochem Pharmacol* **34**: 1120–1121.

Kesteloot H, Oviasu VO, Obasohan AO, Olomu A, Cobbaert C, Lissens W. 1989. Serum lipid and apolipoprotein levels in a Nigerian population sample. *Atherosclerosis* **78**: 33–38.

Kiecolt-Glaser JK, Glaser R, Cacioppo JT, MacCallum RC, Snydersmith M, Kim C, Malarkey WB. 1997. Marital conflict in older adults: Endocrinological and immunological correlates. *Psychosom Med* **59**: 339–349.

Kihara T, Shimohama S, Sawada H, Kimura J, Kume T, Kochiyama H, Maeda T, Akaike A. 1997. Nicotinic receptor stimulation protects neurons against β-amyloid toxicity. *Ann Neurol* **42**: 159–163.

Kilander L, Nyman H, Hansson L, Boberg M, Lithell H. 1999. Cerebrovascular risk factors are determinants of low cognitive function. A 20-year follow-up of 999 elderly men. In *Alzheimer's Disease and Related Disorders*, *Etiology*, *Pathogenesis and Therapeutics*, Iqbal K, Swaab DF, Winblad B, Wisniewski HM (eds). John Wiley & Sons: Chichester; 17–24.

Kim JH, Sharago E, Elson CE. 1988. Age-related changes in respiration coupled to phosphorylation. II. Cardiac mitochondria. *Mech Ageing Dev* **46**: 279–290.

Kim SH, Kim YK, Jeong SJ, Haass C, Kim YH, Suh YH. 1997. Enhanced release of secreted form of Alzheimer's amyloid precursor protein from PC12 cells by nicotine. *Molec Pharmacol* **52**: 430–436.

Kim T-W, Pettingell WH, Jung Y-K, Kovacs DM, Tanzi RE. 1997. Alternative cleavage of Alzheimer-associated presenilins during apoptosis by a caspase-3 family protease. *Science* **277**: 373–376.

Kito S, Shingo AS, Miyoshi R, Kondo K. 1997. Nicotine and estrogen: cross talk in brain in IGF-1 mRNA expression. *Soc Neurosci Abstr* **23**: 1709.

Klunk WE, Panchalingam K, McClure RJ, Stanley JA, Pettegrew JW. 1998. Metabolic alterations in postmortem Alzheimer's disease brain are exaggerated by Apo-E4. *Neurobiol Aging* **19**: 511–515.

Knebl J, DeFazio P, Clearfield M, Little L, McConathy W, Pherson R, Lacko A. 1994. Plasma lipids and cholesterol esterification in Alzheimer's disease. *Mech Aging Dev* **73**: 69–77.

Knott VJ, Harr A. 1997. Aging, smoking and EEG coherence: a preliminary study. *Clin Electroencephalogr* **28**: 236–244.

Kokmen E, Beard CM, Chandra V, Offord KP, Schoenberg BS, Ballard DJ. 1991. Clinical risk factors for Alzheimer's disease: a population-based case-control study. *Neurology* **41**: 1393–1397.

Kokmen E, Whisnant JP, O'Fallon WM, Chu CP, Beard CM. 1996. Dementia after ischemic stroke: a population-based study in Rochester, Minnesota (1960–1984). *Neurology* **46**: 154–159.

Kondo K, Niino M, Shido K. 1994. A case-control study of Alzheimer's disease in Japan — significance of lifestyles. *Dementia* **5**: 314–326.

Kondo Y, Asanuma M, Nishibayashi S, Iwata E, Ogawa N. 1997. Late-onset lipid peroxidation and neuronal death following transient forebrain ischemia in rat brain. *Brain Res* **772**: 37–44.

Kopeikina-Tsiboukidou L, Deliconstantinos G. 1983. Functional changes of rat brain mitochondrial enzymes induced by monomeric cholesterol. *Int J Biochem* **15**: 1403–1407.

Kosaka T, Imagawa M, Seki K, Arai H, Sasaki H, Tsuji S, Asami-Odaka A, Fukushima T, Imai K, Iwatsubo T. 1997. The βAPP 717 Alzheimer mutation increases the percentage of plasma amyloid-β protein ending at Aβ 42(43). *Neurology* **48**: 741–745.

Kosunen O, Talasniemi S, Lehtovirta M, Heinonen O, Helisalmi S, Mannermaa A, Paljarvi L, Ryynanen M, Riekkinen PJ Sr, Soininen H. 1995. Relation of coronary atherosclerosis and apolipoprotein E genotypes in Alzheimer patients. *Stroke* **26**: 743–748.

Koudinov AR, Koudinova NV. 1997. Alzheimer's soluble amyloid beta protein is secreted by HepG2 cells as an apolipoprotein. *Cell Biol Int* **21**: 265–271.

Koudinov AR, Koudinova NV, Berezov TT. 1996a. Alzheimer's peptiodes Aβ 1–40 and Aβ 1–28 inhibit the plasma cholesterol esterification rate. *Biochem Mol Biol Int* **38**: 747–752.

Koudinov AR, Koudinova NV, Kumar A, Beavis RC, Ghiso J. 1996b. Biochemical characterization of Alzheimer's soluble amyloid beta protein in human cerebrospinal fluid: association with high density lipoproteins. *Biochem Biophys Res Commun* **223**: 592–597.

Koudinov AR, Berezov TT, Kumar A, Koudinova NV. 1998a. Alzheimer's amyloid β interaction with normal human plasma high density lipoprotein: association with apolipoprotein amd lipids. *Clin Chim Acta* **270**: 75–84.

Koudinov AR, Berezov TT, Koudinova NV. 1998b. Alzheimer's amyloid beta and lipid metabolism: a missing link?. *FASEB J* **12**: 1097–1099.

Koudinova NV, Berezov TT, Koudinov AR. 1996. Multiple inhibitory effects of Alzheimer's peptide Aβ 1–40 on lipid biosynthesis in cultured human HepG2 cells. *FEBS Lett* **395**: 204–206.

Kovacs DM, Fausett HJ, Page KJ, Kim TW, Moir RD, Merriam DE, Hollister RD, Hallmark OG, Mancini R, Felsenstein KM, Hyman BT, Tanzi RE, Wasco W. 1996. Alzheimer-associated presenilin-1 and presenilin-2: neuronal expression in brain and localization to intracellular membranes in mammalian cells. *Nature Med* **2**: 224–229.

Kratz E, Moffett J, Shetter A, Stachowiak EK, Stachowiak MK. 1997. Activation of the FGF-2 gene by nicotinic acetylcholine and angiotensin II receptors in adrenal medullary cells. *Soc Neurosci Abstr* **23**: 1707.

Krugers HJ, Mulder M, Korf J, Havekes L, de Kloet ER, Joels M. 1997. Altered synaptic plasticity in hippocampal CA1 area of apolipoprotein E deficient mice. *Neuroreport* **8**: 2505–2510.

Kuiper MA, Mulder C, Van Kamp GJH, Scheltens P, Wolters EC. 1994. Cerebrospinal fluid ferritin levels of patients with Parkinson's disease, Alzheimer's disease, and multiple system atrophy. *J Neural Transm Park Dis Dement Sect* **7**: 109–114.

Kumar A, Newberg A, Alavi A, Berlin J, Smith R, Reivich M. 1993. Regional cerebral glucose metabolism in late-life depression and Alzheimer's disease: a preliminary positron emission tomography study. *Proc Natl Acad Sci USA* **90**: 7019–7023.

Kumar R, Agarwal AK, Seth PK. 1996. Oxidative stress-

mediated neurotoxicity of cadmium. *Toxicol Lett* **89**: 65–69.

Kumar A, Jin ZS, Bilker W, Udupa J, Gottlieb G. 1998. Late-onset minor and major depression: early evidence for common neuroanatomical substrates detected by using MRI. *Proc Natl Acad Sci USA* **95**: 7654–7658.

Kung AW, Pang RW, Janus ED. 1995. Elevated serum lipoprotein(a) in subclinical hypothyroidism. *Clin Endocrinol (Oxf)* **43**: 445–449.

Kunugi H. Hattori M, Ueki A, Isse K, Hirasawa H, Nanko S. 1998. Possible association of missense mutation (Gly(-63)Glu) of the neurotrophic-3 gene with Alzheimer's disease in Japanese. *Neursoci Lett* **241**: 65–67.

Kuo YM, Emmerling MR, Bisgaier CL, Essenburg AD, Lampert HC, Drumm D, Roher AE. 1998. Elevated low-density lipoprotein in Alzheimer's disease correlates with brain Aβ 1–42 levels. *Biochem Biophys Res Commun* **252**: 711–715.

Kurumatani T, Kudo T, Ikura Y, Takeda M. 1998. White matter changes in the gerbil brain under chronic cerebral hypoperfusion. *Stroke* **29**: 1058–1062.

Kutryk MJ, Maddaford BR, Pierce GN. 1991. Oxidation of membrane cholesterol alters active and passive transsarcolemmal calcium movement. *Circ Res* **68**: 18–26.

Kuusisto J, Koivisto K, Mykkanen L, Helkaka EL, Vanhanen M, Hanninen T, Kervinen K, Kesaniemi YA, Riekkinen PJ, Laakso M. 1997. Association between features of the insulin resistance syndrome and Alzheimer's disease independently of apolipoprotein E4 phenotype: cross sectional population based study. *Br Med J* **315**: 1045–1049.

Kwan LT, Reed BR, Eberling JL, Schuff N, Tanabe J, Norman D, Weiner MW, Jagust WJ. 1999. Effects of subcortical cerebral infarction on cortical glucose metabolism and cognitive function. *Arch Neurol* **56**: 809–814.

Lacko A, Hayes J, McConathy W, Lacko I, Redheendran R. 1983. Lecithin: cholesterol acyltransferase in Down's syndrome. *Clin Chim Acta* **132**: 133–141.

LaDu MJ, Falduto MT, Manelli AM, Reardon CA, Getz GS, Frail DE. 1994). Isoform-specific binding of apolipoprotein E to β-amyloid. *J Biol Chem* **269**: 23403–23406.

LaDu MJ, Lukens J, Gilligan S, Holtzman DM, Van Eldik LJ, Getz GS, Reardon CA. 1998. β-amyloid associates with CNS lipoproteins. *Soc Neurosci Abstr* **24**: 1712.

LaFerla FM, Hall CK, Ngo L, Jay G. 1996. Extracellular deposition of β-amyloid upon p53-dependent neuronal cell death in transgenic mice. *J Clin Invest* **98**: 1626–1632.

Lai F, Williams RS. 1989. A prospective study of Alzheimer's disease in Down's syndrome. *Arch Neurol* **46**: 849–853.

Lambert JC, Pasquier F, Cottel D, Frigard B, Amouyel P, Chartier-Harlin MC. 1998. A new polymorphism in the APOE promoter associated with risk of developing Alzheimer's disease. *Hum Molec Genetics* **7**: 533–540.

Lamberts SWJ, van den Beld AW, van der Lely A-J. 1997. The endocrinology of aging. *Science* **278**: 419–424.

Landfield PW, Waymire JC, Lynch G. 1978. Hippocampal aging and adrenocorticoids: quantitative correlations. *Science* **202**: 1098–1102.

Lannfelt L, Pedersen NL, Lilius L, Axelman K, Johansson K, Viitanen M, Gatz M. 1995. Apolipoprotein ε 4 allele in Swedish twins and siblings with Alzheimer's disease. *Alzheimer Dis Assoc Disord* **9**: 166–169.

Lansberg J, McDonald B, Watt F. 1992. Absence of aluminum in neuritic plaque cores in Alzheimer's disease. *Nature* **360**: 65–68.

Lantos PL, Luthert PJ, Hanger D, Anderton BH, Mullan M, Rossor M. 1992. Familial Alzheimer's disease with the amyloid precursor protein position 717 mutation and sporadic Alzheimer's disease have the same cytoskeletal pathology. *Neurosci Lett* **137**: 221–224.

Latorraca S, Cecchi C, Iantomasi T, Vincenzini MT, Liguri G, Amaducci L, Sorbi S. 1998. Familial Alzheimer's disease linked to presenilin genes: glutathione levels in lymphoblasts. *Neurobiol Aging* **19**(Suppl. 4): S87.

Launer LJ, Masaki K, Petrovitch H, Foley D, Havlik RJ. 1995. The association between midlife blood pressure levels and late life cognitive function. *J Am Med Assoc* **274**: 1846–1851.

Lauterborn JC, Rivera S, Stinis CT, Hayes VY, Isackson PJ, Gall CM. 1996. Differential effects of protein synthesis inhibition on the activity-dependent expression of BDNF transcripts: evidence for immediate-early gene responses from specific promoters. *J Neurosci* **16**: 7428–7436.

Lee PN. 1994. Smoking and Alzheimer's disease: a review of the epidemiological evidence. *Neuroepidemiology* **13**: 131–144.

Lehmann M, Gottfries CG, Regland B. 1999. Identification of cognitive impairment in the elderly: homocysteine is an early marker. *Dementia Geriatr Cognit Disord* **10**: 12–20.

Lehtonen A, Luutonen S. 1986. High-density lipoprotein cholesterol levels of very old people in the diagnosis of dementia. *Age Ageing* **15**: 267–270.

Lehtovirta M, Kuikka J, Helisalmi S, Hartikainen P, Mannermaa A, Ryynanen M, Riekkinen PS, Soininen H. 1998. Longitudinal SPECT study in Alzheimer's disease: relation to apolipoprotein E polymorphism. *J Neurol Neurosurg Psychiat* **64**: 742–746.

Lejeune J, Turpin R, Gautier M. 1959. Le mongolisme, premier exemple d'aberration autosomique humaine. *Ann Genetique (Paris)* **2**: 41–49.

Lemere CA, Lopera F, Kosik KS, Lendon CL, Ossa J, Saido TC, Yamaguchi H, Ruiz A, Martinez A, Madrigal L, Hincapie L, Arango JCL, Anthony DC, Koo EH, Goate AM, Selkoe DJ, Arango JCV. 1996. The E280A presenilin-1 Alzheimer mutation produces

increased Aβ42 deposition and severe cerebellar pathology. *Nature Med* **2**: 1146–1150.

Lendon CL, Martinez A, Behrens IM, Kosik KS, Madrigal L, Norton J, Neuman R, Myers A, Busfield F, Wragg M, Arcos M, Arango Viana JC, Ossa J, Ruiz A, Goate AM, Lopera F. 1997. E280A PS-1 mutation causes Alzheimer's disease but age of onset is not modified by ApoE alleles. *Hum Mutat* **10**: 186–195.

Leonard JR, Maris DO, Grady MS. 1994. Fluid percussion injury causes loss of forebrain choline acetyltransferase and nerve growth factor receptor immunoreactive cells in the rat. *J Neurotraauma* **11**: 379–392.

Leonard JR, Grady MS, Lee ME, Paz JC, Westrum LE. 1997. Fluid percussion injury causes disruption of the septohippocampal pathway in the rat. *Exp Neurol* **143**: 177–187.

Lesser IM, Mena I, Boone KB, Miller BL, Mehringer CM. Wohl M. 1994. Reduction of cerebral blood flow in older depressed patients. *Arch Gen Psychiat* **51**: 677–686.

Letenneur L, Dartigues JF, Commenges D, Barberger-Gateau P, Tessier JF, Orgogozo JM. 1994. Tobacco consumption and cognitive impairment in elderly people. A population-based study. *Ann Epidemiol* **4**: 449–454.

Leuchter AF, Cook IA, Uijtdehaage SHJ, Dunkin J, Lufkin RB, Anderson-Hanley C, Abrams M, Rosenberg-Thompson S, O'Hara R, Simon SL, Osato S, Babaie A. 1997. Brain structure and function and the outcomes of treatment for depression. *J Clin Psychiat* **58**: 22–31.

Leverenz JB, Raskind MA. 1998. Early amyloid deposition in the medial temporal lobe of young Down's syndrome patients: A regional quantitative study. *Exp Neurol* **150**: 296–304.

Leveugle B, Spik G, Perl DP, Bouras C, Fillit HM, Hof PR. 1994. The iron-binding protein lactotransferrin is present in pathological lesions in a variety of neurodegenerative disorders: a comparative immunohistochemical analysis. *Brain Res* **650**: 20–31.

Levin ED, Simon BB. 1998. Nicotinic acetylcholine involvement in cognitive function in animals. *Psychopharmacology* **138**: 217–230.

Levy A, Dachir S, Arbel I, Kadar T. 1994. Aging, stress, and cognitive function. *Ann NY Acad Sci* **717**: 79–88.

Levy-Lahad E, Wasco W, Poorkaj P, Romano DM, Oshima J, Pettingell WH, Yu C-E, Jondro PD, Schmidt SD, Wang K, Crowley AC, Fu Y-H, Guenette SY, Galas D, Nemens E, Wijsman EM, Bird TD, Schellenberg GD, Tanzi RE. 1995. Candidate gene for the chromosome 1 familial Alzheimer's disease locus. *Science* **269**: 973–977.

Li G, Shen YC, Chen CH, Zhau YW, Li SR, Lu M. 1991. A three-year-follow-up study of age-related dementia in an urban area of Beijing. *Acta Psychiatr Scand* **83**: 99–104.

Li HL, Roch JM, Sundsmo M, Otero D, Sisodia S, Thomas R, Saitoh T. 1997. Defective neurite extension is caused by a mutation in amyloid β/A4 (Aβ) protein precursor found in familial Alzheimer's disease. *J Neurobiol* **32**: 469–480.

Licastro F, Davis LJ, Mocchegiani E, Fabris H. 1996. Impaired peripheral zinc metabolism in patients with senile dementia of probable Alzheimer's type as shown by low plasma concentrations of thymulin. *Biol Trace Elem Res* **51**: 55–62.

Lim PS, Liu CS, Hong CJ, Wei YH. 1997. Prevalence of apolipoprotein E genotypes in ischaemic cerebrovascular disease in end-stage renal disease patients. *Nephrol Dial Transplant* **12**: 1916–1920.

Lin WR, Graham J, MacGowan SM, Wilcock GK, Itzhaki RF. 1998. Alzheimer's disease, herpes virus in brain, apolipoprotein E4 and herpes labialis. *Alzheimer's Reports* **1**: 173–178.

Lindholm D, Castren E, Berzaghi M, Blochl A, Thoenen H. 1994. Activity-dependent and hormonal regulation of neurotrophin messenger RNA levels in the brain: Implication for neuronal plasticity. *J Neurobiol* **25**: 1362–1372.

Liu D, Diorio J, Tannenbaum B, Caldji C, Francis D, Freedman A, Sharma S, Pearson D, Plotsky PM, Meaney MJ. 1997. Maternal care, hippocampal glucocorticoid receptors, and hypothalamic–pituitary–adrenal responses to stress. *Science* **277**: 1659–1662.

Liu H, Miller E, van de Water B, Stevens JL. 1998. Endoplasmic reticulum stress proteins block oxidant-induced Ca^{2+} increases and cell death. *J Biol Chem* **273**: 12858–12862.

Liu HC, Fuh JL, Wang SJ, Liu CY, Larson EB, Lin KN, Wang HC, Chou P, Wu ZA, Lin CH, Wang PN, Teng EL. 1998. Prevalence and subtypes of dementia in a rural Chinese population. *Alzheimer Dis Assoc Disord* **12**: 127–134.

Liu JK, Wang XY, Shigenaga MK, Yeo HC, Mori A, Ames BN. 1996. Immobilization stress causes oxidative damage to lipid, protein, and DNA in the brain of rats. *FASEB J* **10**: 1532–1538.

Liu J, Fischer A, Timiras PS, Ames BN. 1998. Stress, hormones, oxidative damage, and neurodegeneration. *Soc Neurosci Abstr* **24**: 206.

Liu Y, Peterson DA, Schubert D. 1998. Amyloid β peptide alters intracellular vesicle trafficking and cholesterol homeostasis. *Proc Natl Acad Sci USA* **95**: 13266–13271.

Loeffler DA, DeMaggio AJ, Juneau PL, Brickman CM, Mashour GA, Finkelman JH, Pomara H, LeWitt PA. 1994. Ceruloplasmin is increased in cerebrospinal fluid in Alzheimer's disease but not Parkinson's disease. *Alzheimer Dis Assoc Disord* **8**: 190–197.

Loeffler DA, Connor JR, Juneau PL, Snyder BS, Kanaley L, DeMaggio AJ, Nguyen H, Brickman CM. LeWitt PA. 1995. Transferrin and iron in normal, Alzheimer's disease, and Parkinson's disease brain regions. *J Neurochem* **65**: 710–724.

Loeffler DA, LeWitt PA, Juneau PL, Sima AA, Nguyen

HU, DeMaggio AJ, Brickman CM, Brewer GJ, Dick RD, Troyer MD, Kanaley L. 1996. Increased regional brain concentrations of ceruloplasmin in neurodegenerative disorders. *Brain Res* **738**: 265–274.

Lopera F, Ardilla A, Martinez A, Madrigal L, Arango-Viana JC, Lemere CA, Arango-Lasprilla JC, Hincapie L, Arcos-Burgos M, Ossa JE, Behrens IM, Norton J, Lendon C, Goate AM, Ruiz-Linares A, Roselli M, Kosik KS. 1997. Clinical features of early-onset Alzheimer's disease in a large kindred with an E280A presenilin-1 mutation. *JAMA* **277**: 793–799.

Lopen-Alberola RF, Barker WW, Harwood DG, Loewenstein DA, George-Hyslop PH, Tsuda T, Rogaeva EA, Duara R. 1997. Interfamilal and intrafamilial phenotypic heterogeneity in familial Alzheimer's disease. *J. Geriatr Psychiat Neurol* **10**: 1–6.

Lorens SA, Hata N, Handa RJ, Van de Kar LD, Guschwan M, Goral J, Lee JM, Hamilton ME, Bethea CL, Clancy J Jr. 1990. Neurochemical, endocrine and immunological responses to stress in young and old Fischer 344 male rats. *Neurobiol Aging* **11**: 139–150.

Lovell MA, Ehmann WD, Markesbery WR. 1993. Laser microprobe analysis of brain aluminum in Alzheimer's disease. *Ann Neurol* **33**: 36–42.

Lovell MA, Robertson JD, Teesdale WJ, Campbell JL, Markesbery WR. 1998. Copper, iron and zinc in Alzheimer's disease senile plaques. *J Neurol Sci* **158**: 47–52.

Lucassen PJ, Ravid R, Gonatas NK, Swaab DF. 1993. Activation of the human supraoptic and paraventricular nucleus neurons with aging and in Alzheimer's disease disease as judged from increasing size of the Golgi apparatus. *Brain Res* **632**: 105–113.

Lucassen PJ, Salehi A, Pool CW, Gonatas NK, Swaab DF. 1994. Activation of vasopressin neurons in aging and Alzheimer's disease. *J Endocrinol* **6**: 673–679.

Luhmann HJ, Mudrickdonnon LA, Mittmann T, Heinemann U. 1995. Ischemia-induced long-term hyperexcitability in rat neocortex. *Eur J Neurosci* **7**: 180–191.

Luine V, Spencer RL, McEwen BS. 1993. Effect of chronic corticosterone ingestion on spatial memory performance and hippocampal serotonergic function. *Brain Res* **616**: 65–70.

Lund BO, Miller DM, Woods JS. 1993. Studies on Hg(II)-induced H_2O_2 formation and oxidative stress *in vivo* and *in vitro* in rat kidney mitochondria. *Biochem Pharmacol* **45**: 2017–2024.

Lupien S, Lecours AR, Lussier I, Schwartz G, Nair NPV, Meaney MJ. 1994. Basal cortisol-levels and cognitive deficits in human aging. *J Neurosci* **14**: 2893–2903.

Lupien SJ, de Leon M, de Santi S, Convit A, Tarshish C, Thakur M, McEwen BS, Hauger RL, Meaney MJ. 1998. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nature Neurosci* **1**: 69–73.

Luukinen H, Viramo P, Koski K, Laippala P, Kivela SL. 1999. Head injuries and cognitive decline among older adults — A population-based study. *Neurology* **52**: 557–562.

Lyeth BG, Jenkins LW, Hamm RJ, Dixon CE, Phillips LL, Clifton GL, Young HF, Hayes RL. 1990. Prolonged memory impairment in the absence of hippocampal cell death following traumatic brain injury in the rat. *Brain Res* **526**: 249–258.

Lyketsos CG, Chen LS, Anthony JC. 1999. Cognitive decline in adulthood: An 11·5-year follow-up of the Baltimore epidemiologic catchment area study. *Am J Psychiat* **156**: 58–65.

Lyons DM, Martel FL, Levine S, Risch NJ, Schatzberg AF. 1997. Psychosocial stress: postnatal and genetic sources of vulnerability and resilience. *Soc Neurosci Abstr* **23**: 1079.

Maccari S, Piazza PV, Kabbaj M, Barbazanges A, Simon H, Lemoal M. 1995. Adoption reverses the long-term impairment in glucocorticoid feedback induced by prenatal stress. *J Neurosci* **15**: 110–116.

Maes M, Bosmans E, Meltzer HY, Scharpe S, Suy E. 1993. Interleukin-1β: A putative mediator of HPA axis hyperactivity in major depression. *Am J Psychiat* **150**: 1189–1193.

Maestre G, Ottman R, Stern Y, Gurland B, Chun M, Tang MX, Shelanski M, Tycko B, Mayeux R. 1995. Apolipoprotein E and Alzheimer's disease: ethnic variation in genotypic risks. *Ann Neurol* **37**: 254–259.

Magarinos AM. McEwen BS. 1995. Stress-induced atrophy of apical dendrites of hippocampal CA3c neurons: involvement of glucocorticoid secretion and excitatory amino acid receptors. *Neuroscience* **69**: 89–98.

Makino S, Smith MA, Gold PW. 1995. Increased expression of corticotropin-releasing hormone and vasopressin messenger ribonucleic acid (messenger RNA) in the hypothalamic paraventricular nucleus during repeated stress: association with reduction in glucocorticoid receptor messenger RNA levels. *Endocrinology* **136**: 3299–3309.

Makjanic J, McDonald B, Chen CPLH, Watt F. 1998. Absence of aluminium in neurofibrillary tangles in Alzheimer's disease. *Neurosci Lett* **240**: 123–126.

Malin SA, Guo WXA, Jafari G, Goate AM, Nerbonne JM. 1998. Presenilins upregulate function K^+ channel currents in mammalian cells. *Neurobiol Dis* **4**: 398–409.

Malinchoc M, Rocca WA, Colligan RC, Offord KP, Kokmen E. 1997. Premorbid personality characteristics in Alzheimer's disease: an exploratory case-control study. *Eur J Neurol* **4**: 227–230.

Mann DMA. 1993. Association between Alzheimer's disease and Down's syndrome: neuropathological observations. In *Alzheimer's Disease*, *Down's Syndrome and their Relationship*, Berg JM, Karlinsky H, Holland AJ (eds). Oxford Medical Publications: Oxford; 71–92.

Mann DMA, Yates PO, Marcyniuk B, Ravindra CR. 1987. Loss of neurones from cortical and subcortical areas in Down's syndrome patients at middle age. Quantative comparisons with younger Down's pat-

ients and patients with Alzheimer's disease. *J Neurol Sci* **80**: 79–89.

Mann DMA, Iwatsubo T, Cairns NJ, Lantos PL, Nochlin D, Sumi SM, Bird TD, Poorkaj P, Hardy J, Hutton M, Prihar G, Crook R, Rossor MN, Haltia M. 1996. Amyloid-β protein (A-β) deposition in chromosome 14-linked Alzheimer's disease: predominance of A-β42(43). *Ann Neurol* **40**: 149–156.

Mantyh PW, Ghilardi JR, Rogers S, Demaster E, Allen CJ, Stimson ER, Maggio JE. 1993. Aluminum, iron, and zinc promote aggregation of physiological concentrations of β-amyloid peptide. *J Neurochem* **61**: 1171–1174.

Maquire J, Binsack DP, Marotta CA. 1996. Co-expression of apolipoprotein E and amyloid precursor protein following brain injury. *Soc Neurosci Abstr* **22**: 209.

Marambaud P, daCosta CA, Ancolio K, Checler F. 1998. Alzheimer's disease-linked mutation of presenilin 2 (N1411-PS2) drastically lowers APPα secretion: Control by the proteasome. *Biochem Biophys Res Commun* **252**: 134–138.

Marangell LB, Ketter TA, George MS, Pazzaglia PJ, Callahan AM, Parekh P, Andreason PJ, Horwitz B, Herscovitch P, Post RM. 1997. Inverse relationship of peripheral thyrotropin-stimulating hormone levels to brain activity in mood disorders. *Am J Psychiat* **154**: 224–230.

Maret W. 1995. Metallothionein/disulfide interactions, oxidative stress, and the mobilization of cellular zinc. *Neurochem Int* **27**: 111–117.

Marin DB, Breuer B, Marin ML, Silverman J, Schmeidler J, Greenberg D, Flynn S, Mare M, Lantz M, Libow L, Neufeld R, Altstiel L, Davis KL, Mohs RC. 1998. The relationship between apolipoprotein E, dementia, and vascular illness. *Atherosclerosis* **140**: 173–180.

Markesbery WR, Ehmann WD. 1994. Brain trace elements in Alzheimer's Disease. In *Alzheimer's disease*, Terry RD, Katzman R, Bick KL (eds). Raven Press: New York; 353–367.

Marques MA, Tolar M, Harmony JAK, Crutcher KA. 1996. A thrombin cleavage fragment of apolipoprotein E exhibits isoform-specific neurotoxicity. *Neuroreport* **7**: 2529–2532.

Marques MA, Tolar M, Crutcher KA. 1997. Apolipoprotein E neurotoxicity is attenuated by protease inhibitors. *Soc Neurosci Abstr* **23**: 826.

Martel CL, Mackic JB, Matsubara E, Governale S, Miguel C, Miao W, McComb JG, Frangione B, Ghiso J, Zlokovic BV. 1997. Isoform-specific effects of apolipoprotein E2, E3, and E4 on cerebral capillary sequestration and blood–brain barrier transport of circulating Alzheimer's amyloid beta. *J Neurochem* **69**: 1995–2004.

Martin NA, Patwardhan RV, Alexander MJ, Africk CZ, Lee JH, Shalmon E, Hovda DA, Becker DP. 1997. Characterization of cerebral hemodynamic phases following severe head trauma: Hypoperfusion, hyperemia, and vasospasm. *J Neurosurg* **87**: 9–19.

Martinez M, Campion D, Brice A, Hannequin D, Dubois B, Didierjean O, Michon A, Thomas-Anterion C, Puel M, Frebourg T, Agid Y, Clerget-Darpoux F. 1998. Apolipoprotein E epsilon 4 allele and familial aggregation of Alzheimer's disease. *Arch Neurol* **55**: 810–816.

Marty MS, Atchison WD. 1998. Elevations of intracellular Ca^{2+} as a probable contributor to decreased viability in cerebellar granule cells following acute exposure to methylmercury. *Toxicol Appl Pharmacol* **150**: 98–105.

Martyn CN, Barker DJP, Osmond C, Harris EC, Edwardson JA, Lacey RF. 1989. Geographical relation betwen Alzheimer's disease and aluminium in drinking water. *Lancet* **i**: 59–62.

Maruyama K, Tomita T, Shinozaki K, Kume H, Asada H, Saido TC, Ishiura S, Iwatsubo T, Obata K. 1996. Familial Alzheimer's disease-linked mutations at Val^{717} of amyloid precursor protein are specific for the increased secretion of Aβ-42(43). *Biochem Biophys Res Commun* **277**: 730–735.

Masaki KH, White LR, Petrovich H, Ross GW, Curb JD, Ardo E, Grove J. 1994. The influence of prior and concurrent use of aspirin and vitamins on cognitive function scores in elderly Japanese-American men. *Neurobiol Aging* (Suppl. 1): S74.

Masliah E, Mallory M, Ge N, Alford M, Veinbergs I, Roses AD. 1995. Neurodegeneration in the central nervous system of apoE-deficient mice. *Exp Neurol* **136**: 107–122.

Maslih E, Sisk A, Mallory M, Mucke L, Schenk D, Games D. 1996a. Comparison of neurodegenerative pathology in transgenic mice overexpressing V717F β-amyloid precursor protein and Alzheimer's disease. *J Neurosci* **16**: 5795–5811.

Masliah E, Mallory M, Veinbergs I, Miller A, Samuel W. 1996b. Alterations in apolipoprotein E expression during aging and neurodegeneration. *Progr Neurobiol* **50**: 493–503.

Masliah E, Samuel W, Veinbergs I, Mallory M, Mante M, Saitoh T. 1996c. Neurodegeneration and cognitive impairment in apoE-deficient mice is ameliorated by infusion of recombinant apoE. *Soc Neurosci Abstr* **22**: 207.

Mason RP, Shoemaker WJ, Shajenko L, Herbette LG. 1993. X-ray diffraction analysis of brain lipid membrane structure in Alzheimer's disease and β-amyloid peptide interactions. *Ann NY Acad Sci* **695**: 54–58.

Matsui T, Arai H, Nakagawa T, Higuchi M, Okamura N, Tashiro M, Morikawa Y, Sasaki H. 1998. Herpes simplex virus infection as a risk factor of Alzheimer's disease. *Neurobiol Aging* **19**(Suppl. 4): S30.

Matsumoto A. 1994. Altered processing characteristics of β-amyloid-containing peptides in cytosol and in media of familial Alzheimer's disease cells. *Biochim Biophys Acta* **1225**: 304–310.

Mattila KM, Forsell C, Pirttila T, Rinne JO, Lehtimaki T, Roytta M, Lilius L, Eerola A, St George-Hyslop

PH, Frey H, Lannfelt L. 1998. The Glu318Gly mutation of the presenilin-1 gene does not necessarily cause Alzheimer's disease. *Ann Neurol* **44**: 965–967.
Mattson MP. 1997. Mother's legacy: mitochondrial DNA mutations and Alzheimer's disease. *Trends Neurosci* **20**: 373–375.
Mattson MP, Guo Q, Furukawa K, Pedersen WA. 1998. Presenilins, the endoplasmic reticulum, and neuronal apoptosis in Alzheimer's disease. *J Neurochem* **70**: 1–14.
Mauri M, Sinforiani E, Bono G, Vignati F, Berselli ME, Attanasio R, Nappi G. 1993. Memory impairment in Cushing's disease. *Acta Neurol Scand* **87**: 52–55.
Mayberg HS. 1994. Frontal lobe dysfunction in secondary depression. *J Neuropsychiat Clin Neurosci* **6**: 428–442.
Mayeux R, Ottman R, Tang M-X, Noboa-Bauza L, Marder K, Gurland B, Stern Y. 1993. Genetic susceptibility and head injury as risk factors for Alzheimer's disease among community-dwelling elderly persons and their first-degree relatives. *Ann Neurol* **33**: 494–501.
Mayeux R, Ottman R, Maestre G, Ngai C, Tang M-X, Ginsberg H, Chun M, Tycko B, Shelanski M. 1995. Synergistic effects of traumatic head injury and apolipoprotein-ε4 in patients with Alzheimer's disease. *Neurology* **45**: 555–557.
Mayevsky A, Doron A, Manor T, Meilin S, Zarchin N, Ouaknine GE. 1996. Cortical spreading depression recorded from the human brain using a multiparametric monitoring system. *Brain Res* **740**: 268–274.
McAdams C, Leonard BE. 1993. Neutrophil and monocyte phagocytosis in depressed patients. *Progr Neuro-Psychopharmacol Biol Psychiat* **17**: 971–984.
McAllister AK, Katz LC, Lo DC. 1996. Neurotrophin regulation of cortical dendritic growth requires activity. *Neuron* **17**: 1057–1064.
McCaddon A, Kelly CL. 1994. Familial Alzheimer's disease and vitamin B12 deficiency. *Age Ageing* **23**: 334–337.
McDermott JR, Smith AI, Iqbal K, Wisniewski HM. 1979. Brain aluminum in aging and Alzheimer's disease. *Neurology* **29**: 809–814.
McEwen BS, Sapolsky RM. 1995. Stress and cognitive function. *Curr Opin Neurobiol* **5**: 205–216.
McEwen BS, Magarinos AM. 1997. Stress effects on morphology and function of the hippocampus. *Ann NY Acad Sci* **821**: 271–284.
McEwen BS, Gould EA, Sakai RR. 1992. The vulnerability of the hippocampus to protective and destructive effects of glucocorticoids in relation to stress. *Br J Psychiat* **15**(Suppl.): 18–23.
McGeer PL, Walker DG, Pitas RE, Mahley RW, McGeer EG. 1997. Apolipoprotein E4 (ApoE4) but not ApoE3 or ApoE2 potentiates β-amyloid protein activation of complement *in vitro*. *Brain Res* **749**: 135–138.
McLachlan DRC. 1995. Aluminum and the risk for Alzheimer's disease. *Environmetric* **6**: 233–275.
McLachlan DRC, Bergeron C, Smith JE, Boomer D, Rifat SL. 1996. Risk for neuropathologially confirmed Alzheimer's disease and residual aluminum in municipal drinking water employing weighted residential histories. *Neurology* **46**: 401–405.
Meaney MJ, Aitken DH, van Berkel C, Bhatnagar S, Sapolsky RM. 1988. Effect of neonatal handling on age-related impairments associated with the hippocampus. *Science* **239**: 766–768.
Mecocci P, Cherubini A, Beal MF, Cecchetti R, Chionne F, Polidori MC, Romano G, Senin U. 1996. Altered mitochondrial membrane fluidity in AD brain. *Neurosci Lett* **207**: 129–132.
Mecocci P, Beal MF, Cecchetti R, Polidori MC, Cherubini A, Chionne F, Avellini L, Romano G, Senin U. 1997. Mitochondrial membrane fluidity and oxidative damage to mitochondrial DNA in aged and AD human brain. *Molec Chem Neuropathol* **31**: 53–64.
Meguro K, Yamaguchi S, Arai H, Nakagawa T, Doi C, Yamada M, Ikarashi Y, Maruyama Y, Sasaki H. 1994. Nicotine improves cognitive disturbance in senescence-accelerated mice. *Pharmacol Biochem Behav* **49**: 769–772.
Mehta PD, Dalton AJ, Mehta SP, Percy ME, Wisniewski HM. 1993. Increased β_2-microglobulin (β_2-M) and interleukin-6 (IL-6) in sera from older persons with Down's syndrome. In *Alzheimer's Disease and Related Disorders*, Nicolini M, Zatta GF, Corain B (eds). Pergamon Press: Oxford; 95–96.
Melamed E, Mildworf B, Sharav T, Belenky L, Wertman E. 1987. Regional cerebral blood flow in Down's syndrome. *Ann Neurol* **22**: 275–278.
Meldolesi J, Pozzan T. 1998. The endoplasmic reticulum Ca^{2+} store: a view from the lumen. *Trends Biol Sci* **23**: 10–14.
Mendelsohn AB, Belle SH, Stoehr GP, Ganguli M. 1998. Use of antioxidant supplements and its association with cognitive function in a rural elderly cohort: The MoVIES project. *Am J Epidemiol* **148**: 38–44.
Mendez MF. 1995. The neuropsychiatric aspects of boxing. *Int Psychiat Med* **25**: 249–262.
Mendez MF, Underwood KL, Zander BA, Mastri AR, Sung JH, Frey WH. 1992. Risk factors in Alzheimer's disease: a clinicopathologic study. *Neurology* **42**: 770–775.
Merchant C, Tang MX, Albert S, Manly J, Stern Y, Mayeux R. 1999. The influence of smoking on the risk of Alzheimer's disease. *Neurology* **52**: 1408–1412.
Mercken M, Takahashi H, Honda T, Sato K, Murayama M, Nakazato Y, Noguchi K, Imahori K, Takashima A. 1996. Characterization of human presenilin 1 using N-terminal specific monoclonal antibodies: evidence that Alzheimer mutations affect proteolytic processing. *FEBS Lett* **389**: 297–303.
Meyer JS, Akiyama H, Mortel KF, Konno S, Margishvili GM. 1997. Human aging: Risk factors for cerebral atrophy. *Ann NY Acad Sci* **826**: 483–489.

Miao H, Zhang X, Nordberg A. 1997. Nicotine attenuates the cytotoxicity induced by long term treatment with amyloid β protein in PC12 cells. *Soc Neurosci Abstr* **23**: 1893.

Michalopoulou G, Alevizaki M, Piperingos G, Mitsibounas D, Mantzos E, Adamopoulos P, Koutras DA. 1998. High serum cholesterol levels in persons with 'high-normal' TSH levels: should one extend the definition of subclinical hypothyroidism? *Eur J Endocrinol* **138**: 141–145.

Michel PP, Agid Y. 1995. Death of septal cholinergic neurons produced by chronic exposure to glutamate is prevented by the noncompetitive NMDA receptor/channel antagonist, MK-801: role of nerve growth factor and nitric oxide. *J Neurosci Res* **40**: 764–775.

Miller JW. 1999. Homocysteine and Alzheimer's disease. *Nutrit Rev* **57**: 126–129.

Minthon L, Hesse C, Sjogren M, Englund E, Gustafson L, Blennow K. 1997. The apolipoprotein E epsilon4 allele frequency is normal in frontotemporal dementia, but correlates with age at the onset of disease. *Neurosci Lett* **226**: 65–67.

Miranda P, Williams CL, Einstein G. 1999. Granule cells in aging rats are sexually dimorphic in their response to estradiol. *J Neurosci* **19**: 3316–3325.

Miyata M, Smith JD. 1996. Apolipoprotein-E allele-specific antioxidant activity and effects on cytotoxicity by oxidative insults and beta-amyloid peptides. *Nature Genetics* **14**: 55–61.

Mizoguchi K, Kunishita T, Chui DH, Tabira T. 1992. Stress induces neuronal death in the hippocampus of castrated rats. *Neurosci Lett* **138**: 157–160.

Mizuno T, Haass C, Yanagisawa K. 1998. Cholesterol-dependent generation of amyloidogenic β-protein in MDCK cells. *Soc Neurosci Abstr* **24**: 208.

Mocchegiani E, Imberti T, Testasecca D, Zandri M, Santarelli L, Fabris N. 1995. Thyroid and thymic endocrine function and survival in severely traumatized patients with or without head injury. *Intensive Care Med* **21**: 334–341.

Moechars D, Lorent K, De Strooper B, Dewachter I, Van Leuven F. 1996. Expression in brain of amyloid precursor protein mutated in the α-secretase site causes disturbed behavior, neuronal degeneration and premature death in transgenic mice. *EMBO J* **15**: 1265–1274.

Moechars D, Dewachter I, Lorent K, Reverse D, Baekelandt V, Naidu A, Tesseur I, Spittaels K, Van Den Haute C, Checler F, Godaux E, Cordell B, Van Leuven F. 1999. Early phenotypic changes in transgenic mice that overexpress different mutants of amyloid precursor protein in brain. *J Biol Chem* **274**: 6483–6492.

Moghaddam B, Bolinao ML, Stein-Behrens B, Sapolsky RM. 1994. Glucocorticoids mediate the stress-induced extracellular accumulation of glutamate. *Brain Res* **655**: 251–254.

Mohammed AH, Henriksson BG, Soderstrom S, Ebental T, Olsson T, Seckl JR. 1993. Environmental influences on the central nervous system and their implications for the aging rat. *Behav Brain Res* **57**: 183–191.

Moody DM, Brown WR, Challa VR, Ghazi-Birry HS, Reboussin DM. 1997. Cerebral microvascular alterations in aging, leukoaraiosis, and Alzheimer's disease. *Ann NY Acad Sci* **826**: 103–116.

Mooradian AD. 1990. Blood–brain transport of triiodothyronine is reduced in aged rats. *Mech Ageing Dev* **52**: 141–147.

Morgan K, Morgan L, Carpenter K, Lowe J, Lam L, Cave S, Xuereb J, Wischik, Harrington C, Kalsheker NA. 1997. Microsatellite polymorphism of the α_1-antichymotrypsin gene locus associated with sporadic Alzheimer's disease. *Hum Genetics* **99**: 27–31.

Mori E, Hirono N, Yamashita H, Imamura T, Ikejiri Y, Ikeda M, Kitagaki H, Shimomura T, Yoneda Y. 1997. Premorbid brain size as a determinant of reserve capacity against intellectual decline in Alzheimer's disease. *Am J Psychiat* **154**: 18–24.

Morimoto T, Ohsawa I, Takamura C, Ishiguro M, Kohsaka S. 1998. Involvement of amyloid precursor protein in functional synapse formation in cultured hippocampal neurons. *J Neurosci Res* **51**: 185–195.

Moroney JT, Bagiella E, Desmond DW, Paik MC, Stern Y, Tatemichi TK. 1996. Risk factors for incident dementia after stroke: role of hypoxic and ischemic disorders. *Stroke* **27**: 1283–1289.

Morris MC, Beckett LA, Scherr PA, Hebert LE, Bennett DA, Field TS, Evans DS. 1998. Vitamin E and vitamin C supplement use and risk of incident Alzheimer's disease. *Alzheimer Dis Assoc Disord* **12**: 121–126.

Morrison ES, Scott RF, Lee WM, Frick J, Kroms M, Cheney CP. 1977. Oxidative phosphorylation and aspects of calcium metabolims in myocardia of hypercholesterolaemic swine with moderate coronary atherosclerosis. *Cardiovasc Res* **11**: 547–553.

Mortimer JA. 1997. Brain reserve and the clinical expression of Alzheimer's disease. *Geriatrics* **52**: S50–S53.

Mortimer JA, Van Duijn CM, Chandra V, Fratiglioni L, Graves AB, Heyman A, Jorm AF, Kokmen E, Kondo K, Rocca WA, Shalat SL, Soininen H, Hofman A, for the EURODEM Risk Factors Research Group. 1991. Head trauma as a risk factor for Alzheimer's disease: a collaborative reanalysis of case-control studies. *Int J Epidemiol* **20**(Suppl. 2): S13–S20.

Mortimer JA, Fortier I, Rajaram L, Gauvreau D. 1998. Higher education and socioeconomic status in childhood protect individuals at genetic risk of AD from expressing symptoms in late life: The Sageunay-Lac-Saint-Jean Health and Aging Study. *Neurobiol Aging* **19**(Suppl. 4): S215.

Motomura N, Ohkubo F, Asano A, Tomoda Y, Akagi H, Seo T. 1996. Premorbid behavioral characters in demented patients. *Neurobiol Aging* **17**(Suppl. 4): S122.

Moulard B, Sefiani A, Laamri A, Malafosse A, Camu W. 1996. Apolipoprotein-E genotyping in sporadic amyotrophic-lateral-sclerosis — evidence for a major influence on the clinical presentation and prognosis. *J Neurol Sci* **139**(Suppl.): 34–37.

Moya KL, Benowitz LI, Schneider GE, Alliquant B. 1994. The amyloid precursor protein is developmentally regulated and correlated with synaptogenesis. *Develop Biol* **161**: 597–603.

Mucke L, Abraham CR, Masliah E. 1996. Neurotrophic and neuroprotective effects of hAPP in transgenic mice. *Ann NY Acad Sci* **777**: 82–88.

Mudrick LA, Baimbridge KG. 1989. Long-term structural changes in the rat hippocampal formation following cerebral ischemia. *Brain Res* **493**: 179–184.

Muldoon MF, Herbert TB, Patterson SM, Kameneva M, Raibl R, Manuck SB. 1995. Effects of acute psychological stress on serum lipid levels, hemoconcentration, and blood viscosity. *Arch Intern Med* **155**: 615–620.

Muller W, Meske V, Berlin K, Scharnagl H, Marz W, Ohm TG. 1998. Apolipoprotein E isoforms increase intracellular Ca^{2+} differentially through an omega-agatoxin IVa-sensitive Ca^{2+}-channel. *Brain Pathol* **8**: 641–653.

Multhaup G. 1997. Amyloid precursor protein, copper and Alzheimer's disease. *Biomed Pharmacother* **51**: 105–111.

Maurata T, Koshino Y, Omori M, Murata I, Nishio M, Horie T, Umezawa Y, Isaki K, Kimura H, Itoh S, Maeda M, Ishii Y. 1993. *In vivo* proton magnetic resonance spectroscopy study on premature aging in adult Down's syndrome. *Biol Psychiat* **34**: 290–297.

Murdoch I, Perry EK, Court JA, Graham DI, Dewar D. 1998. Cortical cholinergic dysfunction after human head injury. *J Neurotrauma* **15**: 295–305.

Murdoch JC, Ratcliffe WA, McLarty DG, Rodger JC, Ratcliffe JG. 1997. Thyroid function in adults with Down's syndrome. *J Clin Endocrinol Metab* **44**: 453–458.

Murrell J, Farlow M, Ghetti B, Benson M. 1991. A mutation in the amyloid precursor protein associated with hereditary Alzheimer's disease. *Science* **254**: 97–99.

Myers RH, Schaefer EJ, Wilson PW, D'Agostino R, Ordovas JM, Espino A, Au R, White RF, Knoefel JE, Cobb JL, McNulty KA, Beiser A, Wolf PA. 1996. Apolipoprotein E $\varepsilon 4$ association with dementia in a population-based study: The Framingham study. *Neurology* **46**: 673–677.

Nacmias B, Tedde A, Guarnieri BM, Petruzzi C, Ortenzi L, Serio A, Amaducci L, Sorbi S. 1997. Analysis of apolipoprotein E, alpha 1-antichymotrypsin and presenilin-1 genes polymorphisms in dementia caused by normal pressure hydrocephalus in man. *Neurosci Lett* **229**: 177–180.

Nadeau P, Yuan M, Weisgraber K, Yankner BA. 1998. Regulation of amyloid precursor protein metabolism by lipoproteins. *Soc Neurosci Abstr* **14**: 1005.

Nadler V, Biegon A, Beit-Yannai E, Adamchik J, Shohami E. 1995. ^{45}Ca accumulation in rat brain after closed head injury; attenuation by the novel neuroprotective agent HU-211. *Brain Res* **685**: 1–11.

Nagy K, Nagy V, Bertoni-Freddari C, Nagy I. 1983. Alterations of the synaptosomal membrane 'microviscosity' in the brain cortex of rats during aging and centrophenoxine treatment. *Arch Gerontol Geriatr* **2**: 23–29.

Nagy Z, Esiri MM, Jobst KA, Morris JH, King EMF, McDonald B, Joachim C, Litchfield S, Barnetson L, Smith AD. 1997. The effects of additional pathology on the cognitive deficit in Alzheimer's disease. *J Neuropathol Exp Neurol* **56**: 165–170.

Nakai M, Kawamata T, Taniguchi T, Maeda K, Tanaka C. 1996. Expression of apolipoprotein E mRNA in rat microglia. *Neurosci Lett* **211**: 41–44.

Nakano K, Ohta S, Nishimaki K, Miki T, Matuda S. 1997. Alzheimer's disease and DLST genotype. *Lancet* **350**: 1367–1368.

Nakase S, Kitayama I, Soya H, Hamanaka K, Nomura J. 1998. Increased expression of magnocellular arginine vasopressin mRNA in paraventricular nucleus of stress-induced depression-model rats. *Life Sci* **63**: 23–31.

Namekata K, Imagawa M, Terashi A, Ohta S, Oyama F, Ihara Y. 1997. Association of transferrin C2 allele with late-onset Alzheimer's disease. *Hum Genetics* **101**: 126–129.

Nanri M, Kasahara N, Yamamoto J, Miyake H, Watanabe H. 1997. GTS-21, a nicotinic agonist, protects against neocortical neuronal cell loss induced by the nucleus basalis magnocellularis lesion in rats. *Jpn J Pharmacol* **74**: 285–289.

Nappi RE, Sinforiani E, Mauri M, Bono G, Polatti F, Nappi G. 1999. Memory functioning at menopause: Impact of age in ovariectomized women. *Gynecolog Obstetr Invest* **47**: 29–36.

Nathan BP, Bellosta S, Sanan DA, Weisgraber KH, Mahley RW, Pitas RE. 1994. Differential effects of apolipoproteins E3 and E4 on neuronal growth *in vitro*. *Science* **264**: 850–852.

Nee LE, Lippa CF. 1999. Alzheimer's disease in 22 twin pairs 13-year follow-up: Hormonal infectious and traumatic factors. *Dement Geriatr Cognit Disord* **10**: 148–151.

Nee LE, Eldridge R, Sunderland T, Thomas CB, Katz D, Thompson KE, Weingartner H, Weiss H, Julian C, Cohen R. 1987. Dementia of the Alzheimer type: clinical and family study of 22 twin pairs. *Neurology* **37**: 359–363.

Nelson PG, Fields RD, Yu C, Neale EA. 1990. Mechanisms involved in activity-dependent synapse formation in mammalian central nervous system cell cultures. *J Neurobiol* **21**: 138–156.

Nelson PG, Fitzgerald S, Rapoport SI, Neale EA, Galdzicki Z, Dunlap V, Bowers L, von Agoston D. 1997. Cerebral cortical astroglia from the trisomy 16 mouse, a model for Down's syndrome, produce neuronal cholinergic deficits in cell culture. *Proc Natl Acad Sci USA* **94**: 12644–12648.

Nelson WH, Orr WW Jr, Shane SR, Stevenson JM. 1984. Hypothalamic–pituitary–adrenal axis activity and age in major depression. *J Clin Psychiat* **45**: 120–121.

Nemeroff CB, Krishnan KRR. 1992. Neuroendocrine alterations in psychiatric disorders. In *Neuroendocrinology*, Nemeroff CB (ed.). CRC Press: Boca Raton; 413–441.

Neri LC, Hewitt D. 1991. Aluminium, Alzheimer's disease, and drinking water. *Lancet* **338**: 390.

Ness GC. 1991. Thyroid hormone. Basis for its hyocholesterolemic effect. *J Fla Med Assoc* **78**: 383–385.

Newcomer JW, Craft S, Hershey T, Askins K, Bardgett ME. 1994. Glucocorticoid-induced impairment in declarative memory performance in adult humans. *J Neurosci* **14**: 2047–2053.

Nicoll JAR, Roberts GW, Graham DI. 1995. Apolipoprotein E ε4 allele is associated with deposition of amyloid β-protein following head injury. *Nat Med* **1**: 135–137.

Nicoll JAR, Horsburgh K, Graham DI. 1996. Increased neuronal apoE immunoreactivity after acute bain injury due to global hypoxia/ischemia, hypoglycaemia and status epilepticus. *Neurobiol Aging* **17**(Suppl. 4): S135.

Nicotera P, Rossi A. 1993. Molecular mechanisms of metal neurotoxicity. *J Trace Elem Electrolytes Hlth Dis* **7**: 254–256.

Niklowitz WJ. 1975. Neurofibrillary changes after acute experimental lead poisoning. *Neurology* **25**: 927–934.

Nilsson L, Mohammed AK, Henriksson BG, Winblad B, Bergstrom L. 1995. Influence of place learning on somatostatin levels in the rat brain following environmental deprivation. *Regul Pept* **58**: 11–18.

Nilsson P, Hillered L, Ponten U, Ungerstedt U. 1990. Changes in cortical extracellular levels of energy-related metabolites and amino acids following concussive brain injury in rats. *J Cereb Blood Flow Metab* **10**: 631–637.

Nilsson P, Moller L, Koster A, Hollnagel H. 1997. Social and biological predictors of early menopause: a model for premature aging. *J Int Med* **242**: 299–305.

Nitsch RM, Blusztajn JK, Pittas AG, Slack BE, Growdon JH, Wurtman R. 1992. Evidence for a membrane defect in Alzheimer's disease brain. *Proc Natl Acad Sci USA* **89**: 1671–1675.

Nobili F, Rodriguez G, Marenco S, De Carli F, Gambaro M, Castello C, Pontremoli R, Rosadini G. 1993. Regional cerebral blood flow in chronic hypertension. A correlative study. *Stroke* **24**: 1148–1153.

Nochlin D, van Belle G, Bird TD, Sumi SM. 1993. Comparison of the severity of neuropathologic changes in familial and sporadic Alzheimer's disease. *Alzheimer Dis Assoc Disord* **7**: 212–222.

Noisakran S, Halford WP, Veress L, Carr DJJ. 1998. Role of the hypothalamic pituitary adrenal axis and IL-6 in stress-induced reactivation of latent herpes simplex virus type 1. *J Immunol* **160**: 5441–5447.

Nolan KA, Lino MM, Seligmann AW, Blass JP. 1998. Absence of vascular dementia in an autopsy series from a dementia clinic. *J Am Geriatr Soc* **46**: 597–604.

Nordberg A, Winblad B. 1986. Reduced number of [^{3}H] nicotine and [^{3}H] acetylcholine binding sites in the frontal cortex of Alzheimer brains. *Neurosci Lett* **72**: 115–119.

Nordberg A, Lundqvist H, Hartvig P, Lilja A, Langstrom B. 1995. Kinetic analysis of regional (S)(-)11C-nicotine binding in normal and Alzheimer brains — *in vivo* assessment using positron emission tomography. *Alzheimer Dis Assoc Disord* **9**: 21–27.

North P, Fleischer S. 1983. Alteration of synaptic membrane cholesterol/phospholipid ratio using a lipid transfer protein. Effect on γ-aminobutryic acid uptake. *J Biol Chem* **258**: 1242–1253.

Odetti P, Angelini G, Dapino D, Zaccheo D, Garibaldi S, Dagna-Bricarelli F, Piombo G, Perry G, Smith M, Traverso N, Tabaton M. 1998. Early glycoxidation damage in brains from Down's syndrome. *Biochem Biophys Res Commun* **243**: 849–851.

Odio M, Brodish A, Ricardo MJ Jr. 1987. Effects on immune response by chronic stress are modulated by aging. *Brain Behav Immun* **1**: 204–215.

Ogeng'o JA, Cohen DL, Sayi JG, Matuja WB, Chande HM, Kitinya JN, Kimani JK, Friedland RP, Mori H, Kalaria RN. 1996. Cerebral amyloid β protein deposits and other Alzheimer lesions in nondemented elderly East Africans. *Brain Pathol* **6**: 101–107.

Ogunniyi A, Osuntokun B. 1991. Relatively low prevalence of Alzheimer's disease in developing countries and the racial factor in dementia research. *Ethn Dis* **1**: 394–395.

Oitzl MS, Mulder M, Lucassen PJ, Havekes LM, Grootendorst J, de Kloet ER. 1997a. Severe learning deficits in apolipoprotein E knockout mice in a water maze task. *Brain Res* **752**: 189–196.

Oitzl MS, Workel JO, Fluttert M, de Kloet ER. 1997b. Individual differences in vulnerability to age-related cognitive impairment in the rat are emphasized by maternal deprivation. *Soc Neurosci Abstr* **23**: 1793.

Oka A, Takashima S. 1997. Induction of cyclo-oxygenase 2 in brains of patients with Down's syndrome and dementia of Alzheimer type: specific localization in affected neurones and axons. *Neuroreport* **24**: 1161–1164.

Okamoto T, Takeda S, Giambarella U, Murayama Y, Matsui T, Katada T, Matsuura Y, Nishimoto I. 1996. Intrinsic signaling function of APP as a novel target of 3 V642 mutations linked to familial Alzheimer's disease. *EMBO J* **15**: 3769–3777.

Okochi M, Ishii K, Usami M, Sahara M, Kametani F, Tanaka K, Fraser PE, Ikeda M, Saunders AM, Hendriks L, Shoji SI, Nee LE, Martin JJ, Van Broeckhoven C, St George-Hyslop PH, Roses AD, Mori H. 1997. Proteolytic processing of presenilin-1 (PS-1) is not associated with Alzheimer's disease with or without PS-1 mutations. *FEBS Lett* **418**: 162–166.

Olanow CW, Arendash GW. 1994. Metals and free radicals in neurodegeneration. *Current Opin Neurol* **7**: 548–558.

Olichney JM, Sabbagh MN, Hofstetter CR, Galasko D,

Grundman M, Katzman R, Thal LJ. 1997. The impact of apolipoprotein E4 to cause of death in Alzheimer's disease. *Neurology* **49**: 76–81.

Oliveira JRM, Gallindo RM, Maia LGS, Brito-Marques PR, Otto PA, Passos-Bueno MR, Morais MA, Zatz M. 1998. The short variant of the polymorphism within the promoter region of the serotonin transporter gene is a risk factor for late onset Alzheimer's disease. *Molec Psychiat* **3**: 438–441.

Oliver C, Crayton L, Holland A, Hall S, Bradbury J. 1998. A four year prospective study of age-related cognitive change in adults with Down's syndrome. *Psychol Med* **28**: 1365–1377.

O'Meara ES, Kukull WA, Sheppard L, Bowen JD, McCormick WC, Teri L, Pfanschmidt M, Thompson JD, Schellenberg GD, Larson EB. 1997. Head injury and risk of Alzheimer's disease by apolipoprotein E genotype. *Am J Epidemiol* **146**: 373–384.

Oner P, Bekpinar S, Oz B. 1991. Alterations in some lipid components and Ca^{2+} ATPase activity in brain of rats fed an atherogenic diet. *Res Commun Chem Pathol Pharmacol* **72**: 337–345.

Onodera H, Aoki H, Yae T, Kogure K. 1990. Post-ischemic synaptic plasticity in the rat hippocampus after long-term survival: Histochemical and autoradiographic study. *Neuroscience* **38**: 125–136.

Orengo CA, Kunik ME, Molinari VA, Teasdale TA, Workman RH, Yudofsky SC. 1996. Association of serum cholesterol and triglyceride levels with agitation and cognitive function in a geropsychiatry unit. *J Geriatr Psychiat Neurol* **9**: 53–56.

Orgogozo JM, Dartigues JF, Lafont S, Letenneur L, Commenges D, Salamon R, Renaud S, Breteler MB. 1997. Wine consumption and dementia in the elderly: a prospective community study in the Bordeaux area. *Rev Neurol (Paris)* **153**: 185–192.

Ortega RM, Requejo AM, Andres P, Lopez-Sobaler AM, Quintas ME, Redondo MR, Navia B, Rivas T. 1997. Dietary intake and cognitive function in a group of elderly people. *Am J Clin Nutr* **66**: 803–809.

Osterweil D, Syndulko K, Cohen SN, Pettler-Jennings PD, Hershman JM, Cummings JL, Tourtellotte WW, Solomon DH. 1992. Cognitive function in non-demented older adults with hypothyroidism. *J Am Geriatr Soc* **40**: 325–335.

Osuntokun BO, Sahota A, Ogunniyi AO, Gureje O, Baiyewu O, Adeyinka A, Oluwole SO, Komolafe O, Hall KS, Unverzagt FW, Hui SL, Yang M, Hendrie HC. 1995a. Lack of an association between apolipoprotein E $\varepsilon 4$ and Alzheimer's disease in elderly Nigerians. *Ann Neurol* **38**: 463–465.

Osuntokun BO, Ogunniyi A, Junaid TA, Lekwauwa UG. 1995b. Autopsy survey for Alzheimer's disease in Nigerian Africans: a preliminary report. *African J Med Med Sci* **24**: 75–79.

Ott A, Breteler MM, van Harskamp F, Claus JJ, van der Cammen TJ, Grobbee DE, Hofman A. 1995. Prevalence of Alzheimer's disease and vascular dementia: association with education. The Rotterdam Study. *Br Med J* **310**: 970–973.

Ott A, Breteler MM, de Bruyne MC, van Harskamp F, Grobbee DE, Hofman A. 1997. Atrial fibrillation and dementia in a population-based study. The Rotterdam Study. *Stroke* **28**: 316–321.

Ott A, Slooter AJC, Hofman A, van Harskamp F, Witteman JCM, Van Broeckhoven C, van Duijn CM, Breteler MMB. 1998. Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: the Rotterdam Study. *Lancet* **351**: 1840–1843.

Oxenkrug GF, Gurevich D, Siegel B, Dumlao MS, Gershon S. 1989. Correlation between brain–adrenal axis activation and cotnitive impairment in Alzheimer's disease: is there a gender effect? *Psychiat Res* **29**: 169–175.

Oyama F, Cairns NJ, Shimada H, Oyama R, Titani K, Ihara Y. 1994. Down's syndrome: Up-regulation of β-amyloid protein precursor and τ mRNAs and their defective coordination. *J Neurochem* **62**: 1062–1066.

Oyama F, Sawamura N, Kobayashi K, Morishima-Kawashima M, Kuramochi T, Ito M, Tomita T, Maruyama K, Saido TC, Iwatsubo T, Capell A, Walter J, Grunberg L, Ueyama Y, Haass C, Ihara Y. 1998. Mutant presenilin transgenic mouse: Effect on an age-dependent increase of amyloid β-protein 42 in the brain. *J Neurochem* **71**: 313–322.

Page K, Hollister R, Tanzi RE, Hyman BT. 1996. *In-situ* hybridization analysis of presenilin-1 messenger RNA in Alzheimer's disease and in lesioned rat brain. *Proc Natl Acad Sci USA* **93**: 14020–14024.

Paleologos M, Cumming RG, Lazarus R. 1998. Cohort study of vitamin C intake and cognitive impairment. *Am J Epidemiol* **148**: 45–50.

Pallister C, Jung SS, Shaw I, Nalbantoglu J, Gauthier S, Cashman NR. 1997. Lymphocyte content of amyloid precursor protein is increased in Down's syndrome and aging. *Neurobiol Aging* **18**: 97–103.

Palsson S, Aevarsson O, Skoog I. 1999. Depression, cerebral atrophy, cognitive performance and incidence of dementia — Population study of 85-year-olds. *Br J Psychiat* **174**: 249–253.

Pantel J, Schroder J, Essig M, Popp D, Dech H, Knopp MV, Schad LR, Eysenbach K, Backenstrass M, Friedlinger M. 1997. Quantitative magnetic resonance imaging in geriatric depression and primary degenerative dementia. *J Affect Disord* **42**: 69–83.

Pantoni L, Garcia JH. 1997. Cognitive impairment and cellular/vascular changes in the cerebral white matter. *Ann NY Acad Sci* **826**: 92–102.

Pappas BA, de la Torre JC, Davidson CM, Keyes MT, Fortin T. 1996. Chronic reduction of cerebral blood flow in the adult rat: late emerging CA1 cell loss and memory dysfunction. *Brain Res* **708**: 50–58.

Pappolla MA, Chyan YJ, Omar RA, Hsiao K, Perry G, Smith MA, Bozner P. 1998. Evidence of oxidative stress and *in vivo* neurotoxicity of β-amyloid in a transgenic mouse model of Alzheimer's disease: A chronic

oxidative paradigm for testing antioxidant therapies *in vivo*. *Am J Pathol* **152**: 871–877.

Parent A, Linden DJ, Sisodia SS, Borchelt DR. 1999. Synaptic transmission and hippocampal long-term potentiation in transgenic mice expressing FAD-linked presenilin 1. *Neurobiol Disease* **6**: 56–62.

Paris D, Parker TA, Town T, Suo ZM, Fang CH, Humphrey J, Crawford F, Mullan M. 1998a. Role of peroxynitrite in the vasoactive and cytotoxic effects of Alzheimer's β-amyloid(1-40) peptide. *Exp Neurol* **152**: 116–122.

Paris D, Town T, Parker TA, Humphrey J, Mullan M. 1998b. Isoform-specific vasoconstriction induced by apolipoprotein E and modulation of this effect by Alzheimer's β-amyloid peptide. *Neurosci Lett* **256**: 73–76.

Parks RW, Becker RE, Rippey RF, Gilbert DG, Matthews JR, Kabatay E, Young CS, Vohs C, Danz V, Keim P, Collins GT, Zigler SS, Urycki PG. 1996. Increased regional cerebral glucose metabolism and semantic memory performance in Alzheimer's disease: a pilot double blind transdermal nicotine positron emission tomography study. *Neuropsychol Rev* **6**: 61–79.

Pasquier F, Leys D. 1997. Why are stroke patients prone to develop dementia? *J Neurol* **244**: 135–142.

Passant U, Warkentin S, Karlson S, Nilsson K, Edvinsson L, Gustafson L. 1996. Orthostatic hypotension in organic dementia: relationship between blood pressure, cortical blood flow and symptoms. *Clin Auton Res* **6**: 29–36.

Passant U, Warkentin S, Gustafson L. 1997. Orthostatic hypotension and low blood pressure in organic dementia: a study of prevalence and related clinical characteristics. *Int J Geriatr Psychiat* **12**: 395–403.

Patel AJ, Hayashi M, Hunt A. 1987. Selective persistent reduction in choline acetyltransferase activity in basal forebrain of the rat after thyroid deficiency during early life. *Brain Res* **422**: 182–185.

Paul BA, Parker I, Cotman CW, LaFerla FM. 1997. Overexpression of presenilin-1 potentiates Ca^{2+}-mediated responses in *Xenopus* oocytes. *Soc Neurosci Abstr* **23**: 822.

Pauly JR, Collins AC. 1993. An autoradiographic analysis of alterations in nicotinic cholinergic receptors following 1 week of corticosterone supplementation. *Neuroendocrinology* **57**: 262–271.

Pauly JR, Grun EU, Collins AC. 1990. Chronic corticosterone administration modulates nicotine sensitivity and brain nicotinic receptor binding in C3H mice. *Psychopharmacology* **101**: 310–316.

Payami H, Zareparsi S, Montee KR, Sexton GJ, Kaye JA, Bird TD, Yu CE, Wijsman EM, Heston LL, Litt M, Schellenberg GD. 1996. Gender difference in apolipoprotein E-associated risk of familial Alzheimer's disease — a possible clue to the higher incidence of Alzheimer-disease in women. *Am J Hum Genetics* **58**: 803–811.

Payami H, Schellenberg GD, Zareparsi S, Kaye J, Sexton GJ, Head MA, Matsuyama SS, Jarvik LF, Miller B, McManus DQ, Bird TD, Katzman R, Heston L, Norman D, Small GW. 1997. Evidence for association of HLA-A2 allele with onset age of Alzheimer's disease. *Neurology* **49**: 512–518.

Payton M, Riggs KM, Spiro A, Weiss ST, Hu H. 1998. Relations of bone and blood lead to cognitive functions: The VA Normative Aging Study. *Neurotoxicol Teratol* **20**: 19–27.

Pearlson GD, Warren AC, Starkstein SE, Aylward EH, Kumar AJ, Chase GA, Folstein MF. 1990. Brain atrophy in 18 patients with Down's syndrome: a CT study. *Am J Neuroradiol* **11**: 811–816.

Pedersen WA, Guo Q, Hartman BK, Mattson MP. 1997. Nerve growth factor-independent reduction in choline acetyltransferase activity in PC12 cells expressing mutant presenilin-1. *J Biol Chem* **272**: 22397–22400.

Pendergrass AC, Haley BE, Vimy MJ, Winfield SA, Lorscheider FL. 1997. Mercury vapor inhalation inhibits binding of GTP to tubulin in rat brain: Similarity to a molecular lesion in Alzheimer's diseased brain. *Neurotoxicology* **18**: 315–324.

Pepersack T, Garbusinski J, Robbereht J, Beyer I, Willems D, Fuss M. 1999. Clinical relevance of thiamine status amongst hospitalized elderly patients. *Gerontology* **45**: 96–101.

Percy ME, Dalton AJ, Markovic VD, Crapper-McLachlan DR, Gera E, Hummel JT, Rusk AC, Somerville MJ, Andrews DF, Walfish PG. 1990. Autoimmune thyroiditis associated with mild 'subclinical' hypothyroidism in adults with Down's syndrome: a comparison of patients with and without manifestations of Alzheimer's disease. *Am J Med Genetics* **36**: 148–154.

Perez RG, Squazzo SL, Koo EH. 1996. Enhanced release of amyloid β-protein from codon 670/671 Swedish mutant β-amyloid precursor protein occurs in both secretory and endocytic pathways. *J Biol Chem* **271**: 9100–9107.

Pericak-Vance MA, Johnson CC, Rimmler JB, Saunders AM, Robinson LC, D'Hondt EG, Jackson CE, Haines JL. 1996. Alzheimer's disease and apolipoprotein E4 allele in an Amish population. *Ann Neurol* **39**: 700–704.

Pericak-Vance MA, Bass MP, Yamaoka LH, Gaskell PC, Scott WK, Terwedow HA, Menold MM, Conneally PM, Small GW, Vance JM, Saunders AM, Roses AD, Haines JL. 1997. Complete genomic screen in late-onset familial Alzheimer disease: Evidence for a new locus on chromosome 12. *JAMA* **278**: 1237–1241.

Perkins AJ, Hendrie HC, Callahan CM, Gao SJ, Unverzagt FW, Xu Y, Hall KS, Hui SL. 1999. Association of antioxidants with memory in a multiethnic elderly sample. Using the Third National Health and Nutrition Examination Survey. *Am J Epidemiol* **150**: 37–44.

Perl DP, Brody AR. 1980. Alzheimer's disease: X-ray

spectrometric evidence of aluminum accumulation in neurofibrillary tangle-bearing neurons. *Science* **208**: 297–299.

Perlmutter LS, Chui HC. 1990. Microangiopathy, the vascular basement membrane and Alzheimer's disease: a review. *Brain Res Bull* **24**: 677–686.

Perrig WJ, Perrig P, Stahelin HB. 1997. The relation between antioxidants and memory performance in the old and very old. *J Am Geriatr Soc* **45**: 718–724.

Perry EK, Perry RH. 1993. Neurochemical pathology and therapeutic strategies in degenerative dementia. *Int Rev Psychiat* **5**: 363–380.

Perry EK, Court JA, Lloyd S, Johnson M, Griffiths MH, Spurden D, Piggott MA, Turner J, Perry RH. 1996. Beta-amyloidosis in normal aging and transmitter signaling in human temporal lobe. *Ann NY Acad Sci* **777**: 388–392.

Petot GJ, Riedel TM, Cole R, Debanne SM, Koss E, Lerner AJ, Smyth KA, Whitehouse PJ, Friedland RP. 1998. Long term dietary intake patterns influence the development of Alzheimer's disease in a case control study of lifestyle risk factors. *Neurobiol Aging* **19**(Suppl. 4): S27.

Petrovitch H, White L, Masaki KH, Ross GW, Abbott RD, Rodriguez BL, Lu GQ, Burchfiel CM, Blanchette PL, Curb JD. 1998. Influence of myocardial infarction, coronary artery bypass surgery, and stroke on cognitive impairment in late life. *Am J Cardiol* **81**: 1017–1021.

Pham T, Soderstrom S, Henriksson BG, Mohammed AH. 1997. Effects of neonatal stimulation on later cognitive function hippocampal nerve growth factor. *Behav Brain Res* **86**: 113–120.

Pierce JES, Trojanowski JQ, Graham DI, Smith DH, McIntosh TK. 1996. Immunohistochemical characterization of alterations in the distribution of amyloid precursor proteins and β-amyloid peptide after experimental brain injury in the rat. *J Neurosci* **16**: 1083–1090.

Pierce JES, Smith DH, Trojanowski JQ, McIntosh TK. 1998. Enduring cognitive, neurobehavioral and histopathological changes persist for up to one year following severe experimental brain injury in rats. *Neuroscience* **87**: 359–369.

Pietrini P, Dani A, Furey ML, Alexander GE, Freo U, Grady CL, Mentis MJ, Mangot D, Simon EW, Horwitz B, Haxby JV, Schapiro MB. 1997. Low glucose metabolism during brain stimulation in older Down's syndrome subjects at risk for Alzheimer's disease prior to dementia. *Am J Psychiat* **154**: 1063–1069.

Pike JL, Smith TL, Hauger RL, Nicassio PM, Patterson TL, McClintick J, Costlow C, Irwin MR. 1997. Chronic life stress laters sympathetic, neuroendocrine, and immune responsitivity to an acute psychological stressor in humans. *Psychosom Med* **59**: 447–457.

Pirttila T, Lehtimaki T, Rinne J, Mattila K, Frey H, Nikkari T. 1996. The frequency of apolipoprotein E4 allele is not increased in patients with probable vascular dementia. *Acta Neurol Scand* **93**: 352–354.

Pitas RE. 1996. Microtubule formation and neurite extension are blocked by apolipoprotein E4. *Seminars Cell Cev Biol* **7**: 725–731.

Pitas RE, Boyles JK, Lee SH, Foss D, Mahley RW. 1987. Astrocytes synthesize apolipoprotein E and metabolize apolipoprotein E-containing lipoproteins. *Biochim Biophys Acta* **917**: 148–161.

Plaschke K, Ranneberg T, Bauer J, Weigand M, Hoyer S, Bardenheuer HJ. 1997. The effect of stepwise cerebral hypoperfusion on energy metabolism and amyloid precursor protein(APP) in cerebral cortex and hippocampus in the adult rat. *Ann NY Acad Sci* **826**: 502–506.

Plomin R, Owen MJ, McGuffin P. 1994. The genetic basis of complex human behaviors. *Science* **264**: 1733–1739.

Plotsky PM, Owens MJ, Neneroff CB. 1995. Neuropeptide alterations in mood disorders. In *Psychopharmacology: The Fourth Generation of Progress*, Bloom FE, Kupfer DJ (eds). Raven Press: New York; 971–981.

Poduslo SE, Neal M, Herring K, Shelly J. 1998. The apolipoprotein CI A allele as a risk factor for Alzheimer's disease. *Neurochem Res* **23**: 361–367.

Pohjasvaara T, Erkinjuntti T, Ylikoski R, Hietanen M, Vataja R, Kaste M. 1998. Clinical determinants of poststroke dementia. *Stroke* **29**: 75–81.

Poirier J, Baccichet A, Dea D, Gauthier S. 1993a. Cholesterol synthesis and lipoprotein reuptake during synaptic remodelling in hippocampus in adult rats. *Neuroscience* **55**: 81–90.

Poirier J, Davignon J, Bouthillier D, Kogan S, Bertrand P, Gauthier S. 1993b. Apolipoprotein-E polymorphism and Alzheimer's disease. *Lancet* **342**: 697–699.

Popovici D, Mihai N, Urbanavicius V. 1990. Abnormalities of oxidative phosphorylation due to excess or deficiency of thyorid hormones. *Endocrinologie* **18**: 143–147.

Posmantur R, Hayes RL, Dixon CE, Taft WC. 1994. Neurofilament 68 and neurofilament 200 protein levels decrease after traumatic brain injury. *J Neurotrauma* **11**: 533–545.

Post RM, Weiss SRB, Smith M, Rosen J, Frye M. 1995. Stress, conditioning, and the temporal aspects of affective disorders. *Ann NY Acad Sci* **771**: 677–696.

Prange AJ Jr, Garbutt JC, Loosen PT. 1987. The hypothalamic–pituitary–thyroid axis in affective disorders. In *Psychopharmacology: The Third Generation of Progress*, Meltzer HY (ed.). Raven Press: New York; 629–636.

Prasher VP, Chowdhury TA, Rowe BR, Bain SC. 1997. ApoE genotype and Alzheimer's disease in adults with Down's syndrome: meta-analysis. *Am J Ment Retard* **102**: 103–110.

Price DL, Tanzi RE, Borchelt DR, Sisodia SS. 1998. Alzheimer's disease: Genetic studies and transgenic models. *Ann Rev Genetics* **32**: 461–493.

Priest ND, Talbot RJ, Newton D, Day JP, King SJ, Fifield LK. 1998. Uptake by man of aluminium in a public water supply. *Hum Exp Toxicol* **17**: 296–301.

Prigatano GP, Schachter DL (eds). 1991. *Awareness of Deficit after Brain Injury: Clinical and Theoretical Issues*. Oxford University Press: New York.

Prince J, Jia S, Bave U, Anneren G, Oreland L. 1994. Mitochondrial enzyme deficiencies in Down's syndrome. *J Neural Transm Park Dis Dement Sect* **8**: 171–181.

Prince M. 1998. Is chronic low-level lead exposure in early life an etiologic factor in Alzheimer's disease? *Epidemiol* **9**: 618–621.

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

Pritchard W, Robinson J, Guy T. 1992. Enhancement of continuous performance task reaction tuime by smoking in non-deprived smokers. *Psychopharmacology* **108**: 437–442.

Qian ZM, Wang Q. 1998. Expression of iron transport proteins and excessive iron accumulation in the brain in neurodegenerative disorders. *Brain Res Rev* **27**: 257–267.

Queen SA, Feeney DM. 1996. Temporally changing patterns of hippocampal cerebral glucose utilization following sensorimotor cortical contusion in rats. *Brain Res* **724**: 246–250.

Querfurth HW, Wijsman EM, St George-Hyslop PH, Selkoe DJ. 1995. βAPP mRNA transcription is increased in cultured fibroblasts from the familial Alzheimer's disease-1 family. *Brain Res Mol Brain Res* **28**: 319–337.

Raadsheer FC, Van Heerikhuize JJ, Lucassen PJ, Hoogendijk WJG, Tilders FJH, Swaab DF. 1995. Corticotropin-releasing hormone messenger RNA levels in the paraventricular nucleus of patients with Alzheimer's disease and depression. *Am J Psychiat* **152**: 1372–1376.

Raber J O'Shea RD, Bloom FE, Campbell IL. 1997. Modulation of hypothalamic–pituitary–adrenal function by transgenic expression of interleukin-6 in the CNS of mice. *J Neurosci* **17**: 9473–9480.

Racchi M, Baeta R, Salvietti N, Ianna P, Franceschini G, Paoletti R, Fumagalli R, Govoni S, Trabucchi M, Soma M. 1997. Secretory processing of amyloid precursor protein is inhibited by increase in cellular cholesterol content. *Biochem J* **322**: 893–898.

Radcliffe KA, Dani JA. 1998. Nicotinic stimulation produces multiple forms of increased glutamatergic synaptic transmission. *J Neurosci* **18**: 7075–7083.

Raghavan R, Khin-Nu C, Brown AG, Day KA, Tyrer SP, Ince PG, Perry EK, Perry RH. 1994. Gender differences in the phenotypic expression of Alzheimer's disease in Down's syndrome (trisomy 21). *Neuroreport* **5**: 1393–1396.

Raiha I, Tarvonen S, Kurki T, Rajala T, Sourander L. 1993. Relationship between vascular factors and white matter low attenuation of the brain. *Acta Neurol Scand* **87**: 286–289.

Raiha I, Kaprio J, Koskenvuo M, Rajala T, Sourander L. 1996. Alzheimer's disease in Finnish twins. *Lancet* **347**: 573–578.

Raiha I, Kaprio J, KoskenVuo M, Rajala T, Sourander L. 1998. Environmental differences in twin pairs discordant for Alzheimer's disease. *J Neurol Neurosurg Psychiat* **65**: 785–787.

Ramade F, Bayle JD. 1989. Adaptation of the adrenocorticotropic response to chronic intermittent stress was altered by intracerebroventricular infusion of hemicholinium-3. *Neuroendocrinology* **50**: 165–169.

Ramirez-Tortosa MC, Quiles JL, Gil A, Mataix J. 1997. Rabbit liver mitochondria coenzyme Q10 and hydroperoxide levels: an experimental model of atherosclerosis. *Mol Aspects Med* **18**(Suppl.): S233–S236.

Rapoport SI, Pettigrew KD, Schapiro MB. 1991. Discordance and concordance of dementia of the Alzheimer type (DAT) in monozygotic twins indicate heritable and sporadic forms of Alzheimer's disease. *Neurology* **41**: 1549–1553.

Rasmusson DX, Brandt J, Martin DB, Folstein MF. 1995. Head injury as a risk factor in Alzheimer's disease. *Brain Injury* **9**: 213–219.

Rebeck GW, Reiter JS, Strickland DK, Hyman BT. 1993. Apolipoprotein E in sporadic Alzheimer's disease: Allelic variation and receptor interactions. *Neuron* **11**: 575–580.

Reed T, Carmelli D, Swan GE, Breitner JC, Welsh KA, Jarvik GP, Deeb S, Auwerx J. 1994. Lower cognitive performance in normal older adult male twins carrying the apolipoprotein E ε4 allele. *Arch Neurol* **51**: 1189–1192.

Reiman EM, Caselli RJ, Yun LS, Chen K, Bandy D, Minoshima S, Thibodeau SN, Osborne D. 1996. Preclinical evidence of Alzheimer's disease in persons homozygous for the ε4 allele for apolipoprotein E. *N Engl J Med* **334**: 752–758.

Reus V. 1984. Hormonal mediation of the memory disorder in depression. *Drug Dev Res* **4**: 489–495.

Reyland ME, Gwynne JT, Forgez P, Prack MM, Williams DL. 1991. Expression of the human apolipoprotein E gene suppresses steroidogenesis in mouse Y1 adrenal cells. *Proc Natl Acad Sci USA* **88**: 2375–2379.

Reynolds GP, Warner CE. 1988. Amino acid neurotransmitter deficits in adults Down's syndrome brain tissue. *Neurosci Lett* **94**: 224–227.

Richardson JS. 1997. Cerebral microischemia as a potential of the neurodegenerative cascade of Alzheimer's disease. *Ann NY Acad Sci* **826**: 437–439.

Richardson JS, Subbarao KV, Ang LC. 1992. On the possible role of iron-induced free radical peroxidation in neuronal degeneration in Alzheimer's disease. *Ann NY Acad Sci* **648**: 326–327.

Richardson SJ. 1993. The biological basis of the menopause. *Ballieres Clin Endocrinol Metab* **7**: 1–16.

Ridgway EC, Cooper DS, Walker H, Rodbard D, Maloof F. 1981. Peripheral responses to thyroid hormone before and after L-thyroxine therapy in patients with subclinical hypothyroidism. *J Clin Endocrinol Metab* **53**: 1238–1242.

Rifat SL, Eastwood MR, McLachlan DRC, Corey PN. 1990. Effect of exposure of miners to aluminium powder. *Lancet* **336**: 1162–1165.

Riggs JE. 1993. Smoking and Alzheimer's disease: protective effect or differential survival bias? *Lancet* **342**: 793–794.

Risberg J. 1980. Regional cerebral blood flow measurements by ^{133}Xe inhalation: methodology and application in neuropathology and psychiatry. *Brain Language* **9**: 9–34.

Rivnay B, Globerson A, Shinitzky M. 1979. Viscosity of lymphocyte plasma membrane in aging mice and its possible relation to serum cholesterol. *Mech Ageing Dev* **10**: 71–79.

Robakis NK, Ramakrishna N, Wolfe G, Wisniewski HM. 1987. Molecular cloning and characterization of cDNA encoding the cerebrovascular and the neuritic plaque amyloid peptides. *Proc Natl Acad Sci USA* **84**: 4190–4194.

Roberts GW, Gentleman SM, Lynch A, Graham DI. 1991. βA4 amyloid protein deposition in the brain after head injury. *Lancet* **338**: 1422–1423.

Roberts JA, Gilardi KVK, Lasley B, Rapp PR. 1997. Reproductive senescence predicts cognitive decline in aged female monkeys. *Neuroreport* **8**: 2047–2051.

Robinson SR, Zhao W, Ng KT, Clarey J, McRae A. 1997. Ferritin concentration is elevated in the cerebrospinal fluid of patients with Alzheimer's or vascular dementia. *Soc Neurosci Abstr* **23**: 2173.

Rocca WA, Van Duijn CM, Clayton D, Chandra V. Fratiglioni L, Graves AB, Heyman A, Jorm AF, Kokmen E, Kondo K, Mortimer JA, Shalat SL, Soininen H, Hofman A, for the EURODEM Risk Factors Research Group. 1991. Maternal age and Alzheimer's disease: a collaborative re-analysis of case-control studies. *Int J Epidemiol* **20**(Suppl. 2): S21–S27.

Rogaev EI, Sherrington R, Rogaeva EA, Levesque G, Ikeda M, Liang Y, Chi H, Lin C, Holman K, Tsuda T, Mar L, Sorbi S, Nacmias B, Piacentini S, Amaducci L, Chumakov I, Cohen D, Lannfelt L, Fraser PE, Rommens JM, St George-Hyslop PH. 1995. Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene. *Nature* **376**: 775–778.

Rogers KS, Higgins ES, Grogan WM. 1980. Influence of dietary cholesterol on mitochondrial function in the rat. *J Nutr* **110**: 248–254.

Rogers SW, Gahring LC, Collins AC, Marks M. 1998. Age-related changes in neuronal nicotinic acetylcholine receptor subunit alpha 4 expression are modified by long-term nicotine administration. *J Neurosci* **18**: 4825–4832.

Romslo I. 1975. Energy-dependent accumulation of iron by isolated rat liver mitochondria. IV. Relationship to the energy state of the mitochondria. *Biochim Biophys Acta* **387**: 69–79.

Roperch JP, Alvaro V, Prieur S, Tuynder M, Nemani M, Lethrosne F, Piouffre L, Dentron MC, Israeli D, Dausset J, Oren M, Amson R, Telerman A. 1998. Inhibition of presenilin 1 expression is promoted by p53 and p21 (WAF-1) and results in apoptosis and tumor suppression. *Nature Med* **4**: 835–838.

Rosenzweig MR, Bennett EL. 1996. Psychobiology of plasticity: Effects of training and experience on brain and behavior. *Behav Brain Res* **78**: 57–65.

Roses AD, Saunders AM. 1997. ApoE, Alzheimer's disease, and recovery from brain stress. *Ann NY Acad Sci* **826**: 200–212.

Roskams AJ. Connor JR. 1990. Aluminum access to the brain: a role for transferrin and its receptor. *Proc Natl Acad Sci USA* **87**: 9024–9027.

Roskams AJ, Connor JR. 1994. Iron, transferrin, and ferritin in the rat brain during development and aging. *J Neurochem* **63**: 709–716.

Rossor MN, Fox NC, Beck J, Campbell TC, Collinge J. 1996. Incomplete penetrance of familial Alzheimer's disease in a pedigree with a novel presenilin-1 gene mutation. *Lancet* **347**: 1560.

Rubinow DR, Post RM, Savard R. 1984. Cortisol hypersecretion and cognitive impairment in depression. *Arch Gen Psychiat* **41**: 279–283.

Rubinow DR, Davis CL, Post RM. 1992. Somatostatin in neuropsychiatric disorders. In *Somatostatin: Basic and Clinical Aspects of Neuroscience*, vol. 4, Weil C, Muller EE, Thorner MO (eds). Springer: Berlin; 29–42.

Ruff RM, Crouch JA, Troster AI, Marshall LF, Buchsbaum JS, Lottenberg S, Somers LM. 1994. Selected cases of poor outcome following a minor brain trauma — comparing neuropsychological and positron emission tomography assessment. *Brain Injury* **8**: 297–308.

Rumble B, Retallack R, Hilbich C, Simms G, Multhaup G, Martins R, Hockey A, Montgomery P, Beyreuther K, Masters CL. 1989. Amyloid A4 protein and its precursor in Down's syndrome and Alzheimer's disease. *N Engl J Med* **320**: 1446–1452.

Saito S, Kobayashi S, Ohashi Y, Igarashi M, Komiya Y, Ando S. 1994. Decreased synaptic density in aged brains and its prevention by rearing under enriched environment as revealed by synaptophysin contents. *J Neurosci Res* **39**: 57–62.

Saitoh T, Kang D, Mallory M, DeTeresa R, Masliah E. 1997. Glial cells in Alzheimer's disease: Preferential effect of APOE risk on scattered microglia. *Gerontology* **43**: 109–118.

Salehi A, Dubelaar EJG, Mulder M, Swaab DF. 1998. Aggravated decrease in the activity of nucleus basalis neurons in Alzheimer's disease is apolipoprotein E-type dependent. *Proc Natl Acad Sci USA* **95**: 11445–11449.

Salerno JA, Grady C, Mentis M, Gonzalez-Aviles A, Wagner E, Schapiro MB, Rapoport SI. 1995. Brain metabolic function in older men with chronic essential hypertension. *J Gerontol Ser A Biol Sci Med* **50**: M147–M154.

Sandholzer C, Delport R, Vermaak H, Utermann G. 1995. High frequency of the apolipoprotein E ε4 allele in Khoi San from South Africa. *Hum Genetics* **95**: 46–48.

Sapolsky RM. 1993. Potential behavior modification of glucocorticoid damage to the hippocampus. *Behav Brain Res* **57**: 175–182.

Sapolsky RM. 1995. Social subordinance as a marker of hypercortisolism. Some unexpected subtleties. *Ann NY Acad Sci* **771**: 626–639.

Sapolsky RM. 1996. Why stress is bad for your brain. *Science* **273**: 749–750.

Sapolsky RM, Spencer EM. 1997. Insulin-like growth factor I is suppressed in socially subordinate male baboons. *Am J Physiol — Regulatory Integrative Comparative Physiol* **42**: R1346–R1351.

Sapolsky RM, Krey LC, McEwen BS. 1983. The adrenocortical stress-response in the aged male rat: impairment of recovery from stress. *Exp Gerontol* **18**: 55–64.

Sapolsky RM, Krey LC, McEwen BS. 1984. Glucocorticoid-sensitive hippocampal neurons are involved in terminating the adrenocortical stress response. *Proc Natl Acad Sci USA* **81**: 6174–6177.

Sapolsky RM, Krey LC, McEwen BS. 1985. Prolonged glucocorticoid exposure reduces hippocampal neuron number: Implications for aging. *J Neurosci* **5**: 1121–1127.

Sapolsky RM, Alberts SC, Altman J. 1997. Hypercortisolism associated with social subordinance or social isolation among wild baboons. *Arch Gen Psychiat* **54**: 1137–1143.

Sappey-Marinier D, Deicken RF, Fein G, Calabrese G, Hubesch B, Van Dyke C, Dillon WP, Davenport L, Meyerhoff DJ, Weiner MW. 1992. Alterations in brain phosphorus metabolite concentrations associated with areas of high signal intensity in white matter at MR imaging. *Radiology* **183**: 247–256.

Sarkar S, Poonam Y, Bhatnagar D. 1997. Cadmium-induced lipid peroxidation and the antioxidant enzymes in rat tissues: Role of vitamin E and selenium. *Trace Elements Electrolytes* **14**: 41–45.

Satav JG, Katyare SS. 1982. Effect of experimental thyrotoxicosis on oxidative phsophorylation in rat liver, kidney and brain mitochondria. *Molec Cell Endocrinol* **28**: 173–189.

Saunders AM, Strittmatter WJ, Schmechel D, St George-Hyslop PH, Pericak-Vance MA, Joo SH, Rosi BL, Gusella JF, Crapper-MacLachlan DR, Alberts MJ, Hulette C, Crain B, Goldgaber D, Roses AD. 1993. Association of apolipoprotein E allele ε4 with late-onset familial and sporadic Alzheimer's disease. *Neurology* **43**: 1467–1472.

Savory J, Exley C, Forbes WF, Huang Y, Joshi JG, Kruck T, McLachlan DRC, 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 Toxicol Environ Hlth* **48**: 615–635.

Sawiris GP, Sydiskis RJ, Bashirelahi N. 1994. Hormonal modulation of herpes simplex virus replication in a mouse neuroblastoma cell line. *J Clin Lab Anal* **8**: 135–139.

Saxe SR, Snowdon DA, Wekstein MW, Henry RG, Grant FT, Donegan SJ, Wekstein DR. 1995. Dental amalgam and cognitive function in older women: Findings from the Nun Study. *J Am Dental Assoc* **126**: 1495–1501.

Sayi JG, Patel NB, Premkumar DRD, Adem A, Winblad B, Matuja WB, Mtui EP, Gatere S, Friedland RP, Koss E, Kalaria RN. 1997. Apolipoprotein E polymorphism in elderly East Africans. *East African Med J* **74**: 668–670.

Schapiro MB, Ball MJ, Grady CL, Haxby JV, Kaye JA, Rapoport SI. 1988. Dementia in Down's syndrome: cerebral glucose utilization, neuropsychological assessment, and neuropathology. *Neurology* **38**: 938–942.

Schapiro MB, Luxenberg JS, Kaye JA, Haxby JV, Friedland RP, Rapoport SI. 1989. Serial quantitative CT analysis of brain morphometrics in adult Down's syndrome at different ages. *Neurology* **39**: 1349–1353.

Schapiro MB, Grady CL, Kumar A, Herscovitch P, Haxby JV, Moore AM, White B, Friedland RP, Rapoport SI. 1990. Regional cerebral glucose metabolism is normal in young adults with Down's syndrome. *J Cerebral Blood Flow Metab* **10**: 199–206.

Scheuner D, Eckman C, Jensen M, Song X, Citron M, Suzuki N, Bird TD, Hardy J, Hutton M, Kukull W, Larson E, Levy-Lahad E, Viitanen M, Peskind E, Poorkaj P, Schellenberg G, Tanzi R, Wasco W, Lannfelt L, Selkoe D, Younkin S. 1996. Secreted amyloid β-protein similar to that in the senile plaques of Alzheimer's disease is increased *in vivo* by the presenilin 1 and 2 and APP mutations linked to familial Alzheimer's disease. *Nat Med* **2**: 864–870.

Schlegel S, von Bardeleben U, Wiedemann K, Frommberger U, Holsboer F. 1989. Computerized brain tomography measures compared with spontaneous and suppressed plasma cortisol levels in major depression. *Psychoneuroendocrinology* **14**: 209–216.

Schmechel DE, Saunders AM, Strittmatter WJ, Crain BJ, Hulette CM, Joo SH, Pericak-Vance MA, Goldgaber D, Roses AD. 1993. Increased amyloid β-peptide deposition in cerebral cortex as a consequence of apolipoprotein E genotype in late-onset Alzheimer's disease. *Proc Natl Acad Sci USA* **90**: 9649–9653.

Schmidt RH, Grady MS. 1995. Loss of forebrain cholinergic neurons following fluid-percussion injury: implications for cognitive impairment in closed head injury. *J Neurosurg* **83**: 496–502.

Schofield PW, Tan M, Marder K, Bell K, Dooneief G,

Chun M, Sano M, Stern Y, Mayeux R. 1997a. Alzheimer's disease after remote head injury: An incidence study. *J Neurol Neurosurg Psychiat* **62**: 119–124.

Schofield PW, Logroscino G, Andrews HF, Albert S, Stern Y. 1997b. An association between head circumference and Alzheimer's disease in a population-based study of aging and dementia. *Neurology* **49**: 30–37.

Scholz W. 1938. Studien zur Pathologie der Hirngefaße im Senium. In *Proceedings of the Fifth International Congress of Neuropathology*, Zurich; 490–494.

Schroeder F, Woodford JK, Kavecansky J, Wood WG, Joiner C. 1995. Cholesterol domains in biological membranes. *Mol Membr Biol* **12**: 113–119.

Schubert D, Chevion M. 1995. The role of iron in β amyloid toxicity. *Biochem Biophys Res Commun* **216**: 702–707.

Schupf N, Kapell D, Lee JH, Ottman R, Mayeux R. 1994. Increased risk of Alzheimer's disease in mothers of adults with Down's syndrome. *Lancet* **344**: 353–356.

Schupf N, Kapell D, Lee JH, Zigman W, Canto B, Tycko B, Mayeux R. 1996. Onset of dementia is associated with apolipoprotein E ε4 in Down's syndrome. *Ann Neurol* **40**: 799–801.

Schupf N, Kapell D, Nightingale B, Rodriguez A, Tycko B, Mayeux R. 1998. Earlier onset of Alzheimer's disease in men with Down's syndrome. *Neurology* **50**: 991–995.

Schwartz M. Duara R, Haxby J, Grady C, White BJ, Kessler RM, Kay AD, Cutler NR, Rapoport SI. 1983. Down's syndrome in adults: brain metabolism. *Science* **221**: 781–783.

Scott LV, Dinan TG. 1998. Vasopressin and the regulation of hypothalamic–pituitary–adrenal axis function: Implications for the pathophysiology of depression. *Life Sci* **62**: 1985–1998.

Seeman TE, Singer BH, Charpentier P. 1995. Gender differences in patterns of HPA axis response to challenge: MacArthur studies of successful aging. *Psychoneuroendocrinology* **20**: 711–725.

Seeman TE, McEwen BS, Singer BH, Albert MS, Rowe JW. 1997. Increase in urinary cortisol excretion and memory declines: MacArthur studies of successful aging. *J Clin Endocrinol Metab* **82**: 2458–2465.

Selye M. 1976. *Stress in Health and Disease*. Butterworth: Stoneham.

Servatius RJ, Ottenweller JE, Gross JL, Natelson BH. 1993. Persistent plasma cholesterol elevations are produced by one or 3 stressor exposures in rats fed a normal laboratory diet. *Physiol Behav* **53**: 1101–1104.

Seshadri S, Wolf PA, Beiser A, Au R, McNulty K, White R, D'Agostino RB. 1997. Lifetime risk of dementia and Alzheimer's disease — The impact of mortality on risk estimates in the Framingham Study. *Neurology* **49**: 1498–1504.

Shafii M, MacMillan DR, Key MP, Derick AM, Kaufman N, Nahinsky ID. 1996. Nocturnal serum melatonin profile in major depression in children and adolescents. *Arch Gen Psychiat* **53**: 1009–1013.

Shaji S, Promodu K, Abraham T, Roy KJ, Verghese A. 1996. An epidemiological study of dementia in a rural community in Kerala, India. *Br J Psychiat* **168**: 745–749.

Shalat SL, Seltzer B, Pidcock C, Baker EL Jr. 1987. Risk factors for Alzheimer's disease: a case-control study. *Neurology*: 37: 1630–1633.

Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW. 1996. Hippocampal atrophy in recurrent major depression. *Proc Natl Acad Sci USA* **93**: 3908–3913.

Shen J, Bronson RT, Chen DF, Xia WM, Selkoe DJ, Tonegawa D. 1997. Skeletal and CNS defects in presenilin-1-deficient mice. *Cell* **89**: 629–639.

Shen Y. 1992. A case-control study of risk factors on Alzheimer's disease. Multicenter collaborative study in China. *Chung Hua Shen Ching Ching Shen Ko Tsa Chih* **25**: 284–287.

Sherrington R, Rogaev EI, Liang Y, Rogaeva EA, Levesque G, Ikeda M, Chi H, Lin C, Li G, Holman K, Tsuda T, Mar L, Foncin J-F, Bruni AC, Montesi MP, Sorbi S, Rainero I, Pinessi L, Nee L, Chumakov I, Pollen D, Brookes A, Sanseau P, Polinsky RJ, Wasco W, DaSilva HAR, Haines JL, Pericak-Vance MA, Tanzi RE, Roses AD, Fraser PE, Rommens JM, St George-Hyslop PH. 1995. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. *Nature* **375**: 754–760.

Sheu K-FR, Brown AM, Haroutunian V, Kristal BS, Thaler H, Lesser M, Kalaria RN, Relkin NR, Mohs RC, Lilius L, Lannfelt L, Blass JP. 1999a. Modulation by DLST of the genetic risk of Alzheimer's disease in a very elderly population. *Ann Neurol* **45**: 48–53.

Sheu K-FR, Blass JP. 1999. Nuclear DNA mutations, mitochondria, and diseases of nervous system. *Ann NY Acad Sci*, in press.

Sheu K-FR, Brown AM, Kristal BS, Kalaria RN, Lilius L, Lannfelt L, Blass JP. 1999b. A DLST genotype associated with reduced risk for Alzheimer's disease. *Neurology* **52**: 1505–1507.

Shigematsu K, McGeer PL, McGeer EG. 1992. Localization of amyloid precursor protein in selective postsynaptic densities of rat cortical neurons. *Brain Res* **592**: 353–357.

Shima S, Shikano T, Kitamura T, Masuda Y, Tsukumo T, Kanba S, Asai M. 1984. Depression and ventricular enlargement. *Acta Psychiatr Scand* **70**: 275–277.

Shimohama S, Taniguchi T, Fujiwara M, Kameyama M. 1986. Changes in nicotinic and muscarinic cholinergic receptors in Alzheimer-type dementia. *J Neurochem* **46**: 288–293.

Shimohama S, Akaike A, Kimura J. 1996. Nicotine-induced protection against glutamate cytotoxicity: nicotinic cholinergic receptor-mediated inhibition of nitric oxide formation. *Ann NY Acad Sci* **777**: 356–361.

Shimokawa M, Yanagisawa K, Nishiye H, Miyatake T. 1993. Identification of amyloid precursor protein in synaptic plasma membrane. *Biochem Biophys Res Commun*: 240–244.

Shoffner JM, Brown MD, Torroni A, Lott MT, Cabell MF, Mirra SS, Beal MF, Yang C-C, Gearing M, Salvo R, Watts RL, Juncos JL, Hansen LA, Crain BJ, Fayad M, Reckord CL, Wallace DC. 1993. Mitochondrial DNA variants observed in Alzheimer's disease and Parkinson disease patients. *Genomics* **17**: 171–184.

Siegel B, Gurevich D, Oxenkrug GF. 1989. Cognitive impairment and cortisol resistance to dexamethasone suppression in elderly depression. *Biol Psychiat* **25**: 229–234.

Siennicki-Lantz A, Lilja B, Rosen I, Elmstahl S. 1998. Cerebral blood flow in white matter is correlated with systolic blood pressure and EEG in senile dementia of the Alzheimer type. *Dementia Geriatr Cognit Disord* **9**: 29–38.

Siesjo BK, Katsura KI, Zhao Q, Folbergrova J, Pahlmark K, Siesjo P, Smith M-L. 1995. Mechanisms of secondary brain-damage in global and focal ischemia — A speculative synthesis. *J Neurotrauma* **12**: 943–956.

Silverman JM, Raiford K, Edland S, Fillenbaum G, Morris JC, Clark CM, Kukull W, Heyman A. 1994. The Consortium to Establish a Registry for Alzheimer's disease (CERAD). Part VI. Family history assessment: a multicenter study of first-degree relatives of Alzheimer's disease probands and nondemented spouse controls. *Neurology* **44**: 1253–1259.

Simons M, Keller P, DeStrooper B, Beyreuther K, Dotti CG, Simons K. 1998. Cholesterol depletion inhibits the generation of β-amyloid in hippocampal neurons. *Proc Natl Acad Sci USA* **95**: 6460–6464.

Simpson SW, Jackson A, Baldwin RC, Burns A. 1997. Subcortical hyperintensities in late-life depression: acute response to treatment and neuropsychological impairment. *Int Psychogeriatr* **9**: 257–275.

Sinha AK, Pickard MR, Kim KD, Ahmed MT, al Yatama F, Evans IM, Ekins RP. 1994. Perturbation of thyroid hormone homeostatis in the adult and brain function. *Acta Med Austriaca* **21**: 35–43.

Skoog I. 1997. The relationship between blood pressure and dementia: a review. *Biomed Pharmacother* **51**: 367–375.

Skoog I, Lernfelt B, Landahl S, Palmertz B, Andreasson LA, Nilsson L, Persson G, Oden A, Svanborg A. 1996. 15-year longitudinal study of blood pressure and dementia. *Lancet* **347**: 1141–1145.

Skoog I, Hesse C, Aevarsson O, Landahl S, Wahlstrom, Fredman P, Blennow K. 1998a. A population study of apoE genotype at the age of 85: Relation to dementia, cerebrovascular disease, and mortality. *J Neurol Neurosurg Psychiat* **64**: 37–43.

Skoog I, Andreasson LA, Landahl S, Lernfelt B. 1998b. A population-based study on blood pressure and brain atrophy in 85-year-olds. *Hypertension* **32**: 404–409.

Slooter AJ, Tang MX, van Duinj CM, Stern Y, Ott A, Bell K, Breteler MM, Van Broeckhoven C, Tatemichi TK, Tycko H, Hofman A, Mayeux R. 1997. Apolipoprotein E epsilon4 and the risk of dementia with stroke. A population-based investigation. *JAMA* **277**: 818–821.

Slooter AJC, Cruts M, Kalmijn S, Hofman A, Breteler MMB, Van Broeckhoven C, van Duijn CM. 1998. Risk estimates of dementia by apolipoprotein E genotypes from a population-based study: The Rotterdam Study. *Arch Neurol* **55**: 964–968.

Small GW, Mazziotta JC, Collins MT, Baxter LR, Phelps ME, Mandelkern MA, Kaplan A, La Rue A, Adamson CF, Chang L, Guze BH, Corder EH, Saunders AM, Haines JL, Pericak-Vance MA, Roses AD. 1995. Apolipoprotein E type 4 allele and cerebral glucose metabolism in relatives at risk for familial Alzheimer's disease. *JAMA* **273**: 942–947.

Smedman M, Potempska A, Rubenstein R, Ju WA, Ramakrishna N, Denman RB. 1997. Effects of cadmium, copper, and zinc on βAPP processing and turnover in COS-7 and PC12 cells. Relationship to Alzheimer's disease pathology. *Molec Chem Neuropathol* **31**: 13–28.

Smine A, Xu XM, Nishiyama K, Katada T, Gambetti P, Yadav SP, Wu X, Shi YC, Yasuhara S, Homburger V, OkamotoT. 1998. Regulation of brain G-protein G_o by Alzheimer's disease gene presenilin-1. *J Biol Chem* **273**: 16281–16288.

Smith DH, Chen XH, Pierce JES, Wolf JA, Trojanowski JQ, Graham DI, McIntosh TK. 1997. Progressive atrophy and neuron death for one year following brain trauma in the rat. *J Neurotrauma* **14**: 715–727.

Smith MA, Harris PRL, Sayre LM, Perry G. 1997. Iron accumulation in Alzheimer's disease is a source of redox-generated free radicals. *Proc Natl Acad Sci USA* **94**: 9866–9868.

Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. 1997. Brain infarction and the clinical expression of Alzheimer's disease: The Nun Study. *JAMA* **277**: 813–817.

Soininen H, Partanen J, Jousmaki V, Helkala EL, Vanhanen M, Majuri S, Kaski M, Hartikainen P, Riekkinen P Sr. 1993. Age-related cognitive decline and electroencephalogram slowing in Down's syndrome as a model of Alzheimer's disease. *Neuroscience* **53**: 57–63.

Soininen H, Kosunen O, Helisalmi S, Mannermaa A, Paljarvi L, Talasniemi S, Ryynanen M, Riekkinen P. 1995. A severe loss of choline acetyltransferase in the frontal cortex of Alzheimer patients carrying apolipoprotein epsilon-4 allele. *Neurosci Lett* **187**: 79–82.

Soneira CF, Scott TM. 1996. Severe cardiovascular disease and Alzheimer's disease: senile plaque formation in cortical areas. *Clin Anat* **9**: 118–127.

Song C, Dinan T, Leonard BE. 1994a. Changes in immunoglobulin, complement and acute-phase protein levels in the depressed patients and normal controls. *J Affect Disord* **30**: 283–288.

Song C, Kelly JP, Leonard BE. 1994b. The effect of stressful behavioral exposure on endocrine and immune parameters in the rat. *Stress Med* **10**: 239–245.

Sorbi S, Piacentini S, Latorraca S, Piersanti P, Amaducci L. 1995. Alterations in metabolic properties in fibroblasts in Alzheimer's disease. *Alzheimer Dis Assoc Disord* **9**: 73–77.

Spady DK, Dietschy JM. 1983. Sterol synthesis *in vivo* in 18 tissues of the squirrel, monkey, guinea pig, rabbit, hamster and rat. *J Lipid Res* **24**: 303–315.

Sparks DL. 1996a. Intraneuronal β-amyloid immunoreactivity in the CNS. *Neurobiol Aging* **17**: 291–299.

Sparks DL. 1996b. Increase cholesterol in AD and cCAD cortex, and increased cholesterol content and free radical enzyme activity in rabbit brain due to dietary cholesterol. *J Neuropathol Exp Neurol* **55**: 618.

Sparks DL. 1997a. Dietary cholesterol induces Alzheimer-like β-amyloid immunoreactivity in rabbit brain. *Nutrit Metab Cardiovasc Dis* **7**: 255–266.

Sparks DL. 1997b. Coronary artery disease, hypertension, ApoE, and cholesterol: a link to Alzheimer's disease? *Ann NY Acad Sci* **826**: 128–146.

Sparks DL, Hunsaker JC, Scheff SW, Kryscio RJ, Henson JL, Markesbery WR. 1990. Cortical senile plaques in coronary artery disease, aging, and Alzheimer's disease. *Neurobiol Aging* **11**: 601–607.

Sparks DL, Scheff SW, Liu H, Landers TM, Coyne CM, Hunsaker JC. 1995. Increased incidence of neurofibrillary tangles (NFT) in non-demented individuals with hypertension. *J Neurol Sci* **131**: 162–169.

Spencer CP, Godsland IF, Stevenson JC. 1997. Is there a menopausal metabolic syndrome? *Gynecol Endocrinol* **11**: 341–355.

Srivastava RAK, Bhasin N, Srivastava N. 1996. Apolipoprotein E gene-expression in various tissues of mouse and regulation by estogen. *Biochem Molec Biol Int* **38**: 91–101.

St George-Hyslop PH, Tanzi RE, Polinsky RJ, Haines JL, Nee L, Watkins PC, Myers RH, Feldman RG, Pollen D, Drachman D, Growdon J, Bruni A, Foncin J-F, Salmon D, Frommelt P, Amaducci L, Sorbi S, Piacentini S, Stewart GD, Hobbs WJ, Conneally PM, Gusella JF. 1987. The genetic defect causing familial Alzheimer's disease maps on chromosome 21. *Science* **235**: 885–890.

Stabel-Burow J, Kleu A, Schuchmann S, Heinemann U. 1997. Glutathione levels and nerve cell loss in hippocampal cultures from trisomy 16 mouse — a model of Down's syndrome. *Brain Res* **765**: 313–318.

Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhager WH, Bulpitt CJ, de Leeuw PW, Dollery CT, Fletcher AE, Forette F, Leonetti G, Nachev C, O'Brient ET, Rosenfeld J, Rodicio JL, Tuomilehto J, Zanchetti A. 1997. Randomized double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial. *Lancet* **350**: 757–764.

Stahelin HB, Staub JJ, Hew-Winzeler AM, Seiler WO, Girard J. 1982. TRH-TSH regulation in the aged and in patients with senile dementia. *Schweiz Med Wochenschr* **112**: 1784–1786.

Starkman MN, Gebarski SS, Berent S, Schteingart DE. 1992. Hippocampal formation volume, memory dysfunction, and cortisol levels in patients with Cushing's syndrome. *Biol Psychiat* **32**: 756–765.

Steffens DC, Plassman BL, Helms MJ, Welsh-Bohmer KA, Saunders AM, Breitner JCS. 1997. A twin study of late-onset depression and apolipoprotein E ε4 as risk factors for Alzheimer's disease. *Biol Psychiat* **41**: 851–856.

Steiger A, Holsboer F. 1997. Nocturnal secretion of prolactin and cortisol and the sleep EEG in patients with major endogenous depression during an acute episode and after full remission. *Psychiat Res* **72**: 81–88.

Stein SA, Kirkpatrick LL, Shanklin DR, Adams PM, Brady ST. 1991. Hypothyroidism reduces the rate of slow component A (Sca) axonal transport and the amount of transported tubulin in the hyt/hyt mouse optic nerve. *J Neurosci Res* **28**: 121–133.

Stein-Behrens BA, Lin WJ, Sapolsky RM. 1994. Physiological elevations of glucocorticoids potentiate glutamate accumulation in the hippocampus. *J Neurochem* **63**: 596–602.

Stern Y, Gurland B, Tatemichi TK, Tang MX, Wilder D, Mayeux R. 1994. Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA* **271**: 1004–1110.

Stevens M, van Duijn CM, de Knijff P, van Broeckhoven C, Heutink P, Oostra BA, Niermeijer MF, van Swieten JC. 1997. Apolipoprotein E gene and sporadic frontal lobe dementia. *Neurology* **48**: 1526–1529.

Stewart R. 1998. Cardiovascular factors in Alzheimer's disease. *J Neurol Neurosurg Psychiat* **65**: 143–147.

Stohs SJ, Bagchi D. 1995. Oxidative mechanisms in the toxicity of metal ions. *Free Radic Biol Med* **18**: 321–336.

Stone DJ, Rozovsky I, Morgan TE, Anderson CP, Hajian H, Finch CE. 1997. Astrocytes and microglia respond to estrogen with increased apoE mRNA *in vivo* and *in vitro*. *Exp Neruol* **143**: 313–318.

Strandgaard S, Paulson OB. 1994. Cerebrovascular consequences of hypertension. *Lancet* **344**: 519–521.

Strassburger TL, Lee HC, Daly EM, Szczepanik J, Krasuski JS, Mentis MJ, Salerno JA, De Carli C, Schapiro MB, Alexander GE. 1997. Interactive effects of age and hypertension on volumes of brain structures. *Stroke* **28**: 1410–1417.

Streit WJ, Sparks DL. 1997. Activation of microglia in the brains of humans with heart disease and hypercholesterolemic rabbits. *J Molec Med* **75**: 130–138.

Strittmatter WJ, Saunders AM, Goedert M, Weisgraber KH, Dong LM, Jakes R, Huang DY, Pericak-Vance M, Schmechel D, Roses AD. 1994. Isoform-specific interactions of apolipoprotein E with microtubule-associated protein tau: Implications for Alzheimer's disease. *Proc Natl Acad Sci USA* **91**: 11183–11186.

Sturchler-Pierrat C, Abramowski D, Duke M, Wiederhold KH, Mistl C, Rothacher S, Ledermann B, Burki K, Frey P, Paganetti PA, Waridel C, Calhoun ME, Jucker M, Probst A, Staufenbiel M, Sommer B. 1997. Two amyloid precursor protein transgenic mouse models with Alzheimer's disease-like pathology. *Proc Natl Acad Sci USA* **94**: 13287–13292.

Subramanian M, Pusphendran CK, Tarachand U, Devasagayam TP. 1993. Gestation confers temporary resistance to peroxidation in the maternal brain. *Neurosci Lett* **155**: 151–154.

Sugawa M, Coper H, Schulze G, Yamashina I, Krause F, Dencher NA. 1996. Impaired plasticity of neurons in aging. Biochemical, biophysical, and behavioral studies. *Ann NY Acad Sci* **786**: 274–282.

Sulkava R, Notkola I-L, Pekkanen J, Ehnholm C, Kivinen P, Tuomilehto J, Nissinen A. 1998. Serum total cholesterol, apolipoprotein E ε4 allele, and Alzheimer's disease. *Neurobiol Aging* **19**(Suppl 4): S245.

Suo ZM, Tan J, Placzek A, Crawford F, Fang CH, Mullan M. 1998. Alzheimer's β-amyloid peptides induce inflammatory cascade in human vascular cells: the roles of cytokines and CD40. *Brain Res* **807**: 110–117.

Surchev L, Dontchev V, Ichev K, Dolapchieva S, Bozhilova-Pastirova A, Vankova M, Kirazov E, Vassiveva E, Venkov L. 1995. Changes in the neuronal plasma membrane during synaptogenesis. *Cell Molec Biol (Noisy-le-grand)* **41**: 1073–1080.

Sutker PB, Winstead DK, Galina ZH, Allain AN. 1991. Cognitive deficits and psychopathology among former prisoners of war and combat veterans of the Korean conflict. *Am J Psychiat* **148**: 67–72.

Suzuki N, Cheung TT, Cai X-D, Odaka A, Otvos L, Eckman C. Golde TE, Younkin SG. 1994. An increased percentage of long amyloid β-protein secreted by familial amyloid β-protein precursor (βAPP717) mutants. *Science* **264**: 1336–1340.

Svennerholm L, Gottfries CG. 1994. Membrane lipids, selectively diminished in Alzheimer brains, suggest synapse loss as a primary event in early-onset (type I) and demyelination in late-onset (Type II). *J Neurochem* **62**: 1039–1047.

Svensson A, Warpman U, Hellstrom-Lindhal E, Bogdanovic N, Lannfelt L, Nordberg A. 1997. Nicotinic receptors, muscarinic receptors and choline acetyltransferase activity in the temporal cortex of Alzheimer patients with differing apolipoprotein E genotypes. *Neurosci Lett* **232**: 37–40.

Swaab DF. 1991. Brain ageing and Alzheimer's disease: 'wear and tear' versus 'use it or lose it'. *Neurobiol Aging* **12**: 317–324.

Sweep CG, van der Meer MJ, Hermus AR, Smals AG, van der Meer JW, Pesman GJ, Willemsen SJ, Benraad TJ, Kloppenborg PW. 1992. Chronic stimulation of the pituitary–adrenal axis in rats by interleukin-1β infusion: *in vivo* and *in vitro* studies. *Endocrinology* **130**: 1153–1164.

Tacconi MT, Cizza G, Fumagalli G, Sarzi Sartori P, Salmona M. 1991. Effect of hypothyroidism induced in adult rats on brain membrane fluidity and lipid content and composition. *Res Commun Chem Pathol Pharmacol* **71**: 85–103.

Takami K, Terai K, Matsuo A, Walker DG, McGeer PL. 1997. Expression of presenilin-1 and -2 mRNAs in rat and Alzheimer's disease brains. *Brain Res* **748**: 122–130.

Takashima S, Iida K, Mito T, Arima M. 1994. Dendritic and histochemical development and ageing in patients with Down's syndrome. *J Intellect Disab Res* **38**: 265–273.

Takeda M, Kanayama G, Niigawa H, Tanii H, Taniguchi N, Ikura Y, Kashiwagi Y, Miyamae Y, Nishimura T. 1997. Nueorchemical basis of risk factors for Alzheimer's disease: acute-phase protein and neurofilament phosphorylation after repetitive subthreshold brain injury. In *Alzheimer's Disease: Biology*, *Diagnosis and Therapeutics*, Iqbal K, Winblad B, Nishimura T, Takeda M, Wisniewski HM (eds). John Wiley: Chichester; 561–566.

Talmi M, Carlier E, Soumireu-Mourat B. 1993. Similar effects of aging and corticosterone treatment on mouse hippocampal function. *Neurobiol Aging* **14**: 239–244.

Talmi M, Carlier E, Bengelloun W, Soumireu-Mourat B. 1996. Chronic RU486 treatment reduces age-related alterations of mouse hippocampal function. *Neurobiol Aging* **17**: 9–14.

Talpade D, Betarbet R, Greenamyre JT, Pettus E, Guido T, Games D. 1998. Profound mitochondrial dysfunction in transgenic mice overexpressing V717F β-amyloid precursor protein. *Soc Neurosci Abstr* **24**: 729.

Tamaoka A, Fraser PE, Ishii K, Sahara N, Ozawa K, Ikeda M, Saunders AM, Komatsuzaki Y, Sherrington R, Levesque G, Yu G, Rogaeva E, Shoji S, Nee LE, Pollen DA, Hendriks L, Martin JJ, Van Broeckhoven C, Roses AD, Farrer LA, St George-Hyslop PH, Mori H. 1998. Amyloid-β-protein isoforms in brain of subjects with PS1-linked, βAPP-linked and sporadic Alzheimer's disease. *Molec Brain Res* **56**: 178–185.

Tang MX, Maestre G, Tsai WY, Liu XH, Feng L, Chung WY, Chun M, Schofield P, Stern Y, Tycko B, Mayeux R. 1996. Effect of age, ethnicity, and head injury on the association between APOE genotypes and Alzheimer's disease. *Ann NY Acad Sci* **802**: 6–15.

Tanimukai H, Imaizumi K, Kudo T, Katayama T, Tsuda M, Takagi T, Tohyama M, Takeda M. 1998. Alzheimer-associated presenilin-1 gene is induced in gerbil hippocampus after transient ischemia. *Molec Brain Res* **54**: 212–218.

Tannenbaum BM, Lupien S, Ohashi E, Meaney MJ. 1996. Daily salivary cortisol levels in healthy elderlies: relationship to dietary lifestyle. *Soc Neurosci Abstr* **22**: 1889.

Tannenbaum BM, Koerner N, Mercier N, Mushynski A, Meaney MJ. 1997a. Basal and stress-induced changes in cortisol in young humans: relationship to food intake. *Soc Neurosci Abstr* **23**: 1242.

Tannenbaum BM, Brindley DN, Tannenbaum GS, Dallman MF, McArthur MD, Meaney MJ. 1997b. High-fat feeding alters both basal and stress-induced hypothalamic–pituitary–adrenal activity in the rat. *Am J Physiol* **273**: E1168–E1177.

Tanner HA. 1995. Bioenergetics in the pathogenesis, progression and treatment of cardiovascular disorders. *Med Hypotheses* **44**: 347–358.

Tanzi RE, Gusella JF, Watkins PC, Bruns GA, St George-Hyslop P, Van Keuren ML, Patterson D, Pagan S, Kurnit DM, Neve RL. 1987. Amyloid β protein gene: cDNA, mRNA distribution, and genetic linkage near the Alzheimer locus. *Science* **235**: 880–884.

Tardiff BE, Newman MF, Saunders AM, Strittmatter WJ, Blumenthal JA, White WD, Croughwell ND, Davis RD, Roses AD, Reves JG, Baldwin B, de Long E, Kirchner JL, Grocott H, Leone BJ, Babak M, Burker E, Fraser H, Mahanna EP, Thyrum EA, Clancey CP, Davis D, Glower DD, Jones RH, Landolfo KP, Smith PK, Clapp-Channing N, Hurwitz BJ, Mark DB, Spillane W. 1997. Preliminary report of a genetic basis for cognitive decline after cardiac operations. *Ann Thoracic Surg* **64**: 715–720.

Tarin JJ, Brines J, Cano A. 1998. Long-term effects of delayed parenthood. *Hum Reprod* **13**: 2371–2376.

Tariska P, Klein V, Panczel G, Vitrai J, Knolmayer J, Meszaros A, Urbanics K, Kiss E. 1997. Vascular disease risk factors and findings in patients with Alzheimer's disease. *Arch Gerontol Geriatr* **25**: 237–243.

Tatebayashi Y, Takeda M, Kashiwagi Y, Okochi M, Kurumadani T, Sekiyama A, Kanayama G, Hariguchi S, Nishimura T. 1995. Cell-cycle-dependent abnormal calcium response in fibroblasts from patients with familial Alzheimer's disease. *Dementia* **6**: 9–16.

Tatemichi TK, Desmond DW, Paik M, Figueroa M, Gropen TI, Stern Y, Sano M, Remien R, Williams JBW, Mohr JP, Maveux R. 1993. Clinical determinants of dementia related to stroke. *Ann Neurol* **33**: 568–575.

Tatemichi TK, Desmond DW, Stern Y, Paik M, Sano M, Bagiella E. 1994a. Cognitive impairment after stroke: Frequency, patterns, and relationship to functional abilities. *J Neurol Neurosurg Psychiat* **57**: 202–207.

Tatemichi TK, Paik M, Bagiella E, Desmond DW, Stern Y, Sano M, Hauser WA, Mayeux R. 1994b. Risk of dementia after stroke in a hospitalized cohort: results of a longitudinal study. *Neurology* **44**: 1885–1891.

Tatemichi TK, Paik M, Bagiella E, Desmond DW, Pirro M, Hanzawa LK. 1994c. Dementia after stroke is a predictor of long-term survival. *Stroke* **25**: 1915–1919.

Teasdale GM, Nicoll JAR, Murray G, Fiddes M. 1997. Association of apolipoprotein E polymorphism with outcome after head injury. *Lancet* **350**: 1069–1071.

Teller JK, Russo C, DeBusk LM, Angelini G, Zaccheo D, Dagna-Bricarelli F, Scartezzini P, Bertolini S, Mann DM, Tabaton M, Gambetti P. 1996. Presence of soluble amyloid β-peptide precedes amyloid plaque formation in Down's syndrome. *Nat Med* **2**: 93–95.

Terry AV, Clarke MSF. 1994. Nicotine stimulation of nerve growth factor receptor expression. *Life Sci* **55**: PL91–PL98.

Teter B, Harris-White ME, Frautschy SA, Gilbert JR, Xu P-T, Roses AD, Galasko D, Cole GM. 1998. Mouse and human apoE and estrogen modulate mossy fiber sprouting in organotypic hippocampel slice culture. *Soc Neurosci Abstr* **24**: 1713.

Thinakaran G, Borchelt DR, Lee MK, Slunt HH, Spitzer L, Kim G, Ratovitsky T, Davenport F, Norstedt C, Seeger M, Hardy J, Levey A, Gandy SE, Jenkins NA, Copeland NG, Price DL, Sisodia SS. 1996. Endoproteolysis of presenilin 1 and accumulation of processed derivatives *in vivo*. *Neuron* **17**: 181–190.

Thinakaran G, Harris CL, Ratovitski T, Davenport F, Slunt HH, Price DL, Borchelt DR, Sisodia SS. 1997. Evidence that levels of presenilins (PS1 and PS2) are coordinately regulated by competition for limiting cellular factors. *J Biol Chem* 28415–28422.

Thomas T, Thomas G, McLendon C, Sutton T, Mullan M. 1996. β-Amyloid-mediated vasoactivity and vascular endothelial damage. *Nature*. **380**: 168–171.

Thomas WE, Crespo-Armas A, Mowbray J. 1987. The influence of nanomolar calcium ions and physiological levels of thyorid hormone on oxidative phosphorylation in rat liver mitochondria. A possible signal amplification control mechanism. *Biochem J* **247**: 315–320.

Thompson CM, Markesbery WR, Ehmann WD, Vance DE. 1988. Regional brain trace element studies in Alzheimer's disease. *Neurotoxicology* **9**: 1–8.

Thorsell A, Svensson P, Wiklund L, Sommer W, Ekman R, Heilig M. 1998. Suppressed neuropeptide Y (NPY) mRNA in rat amygdala following restraint stress. *Regul Pept* **75–76**: 247–254.

Tiberghien D, Robitaille Y, Laroche-Cholette A, Houde L, Genon M, Gauvreau D. 1993. Retrospective assessment of relative risks of coronary arteriosclerosis and myocardial infarct in autopsy-confirmed dementias of the AD and non-AD types. In *Alzheimer's Disease: Advances in Clinical and Basic Research*, Corain B, Iqbal K, Nicolini M, Winblad B, Wisniewski H, Zatta P (eds). John Wiley: Chichester; 121–127.

Timiras PS. 1995. Education, homeostasis, and longevity. *Exp Gerontol* **30**: 189–198.

Tizabi Y, Gilad VH, Gilad GM. 1989. Effects of chronic stressors or corticosterone treatment on the septohippocampal cholinergfic system of the rat. *Neurosci Lett* **105**: 177–182.

Tohgi H, Takahashi S, Kato E, Homma A, Niina R, Sasaki K, Yonezawa M. 1997. Reduced size of right hippocampus in 39- to 80-year-old normal subjects carrying the apolipoprotein E ε4 allele. *Neurosci Lett* **236**: 21–24.

Tohgi H, Yonezawa H, Takahashi S, Sato N, Kato E, Kudo M, Hatano K, Sasaki T. 1998. Cerebral blood flow and oxygen metabolism in senile dementia of Alzheimer's type and vascular dementia with deep white matter changes. *Neuroradiol* **40**: 131–137.

Tokuda T, Fukushima T, Ikeda S, Sekijima Y, Shoji S, Yanagisawa N, Tamaoka A. 1997. Plasma levels of amyloid β proteins Aβ 1–40 and Aβ 1–42(43) are elevated in Down's syndrome. *Ann Neurol* **41**: 271–273.

Tokuhiro S, Tomita T, Awata H, Kosaka T, Saido TC, Maruyama K, Iwatsubo T. 1998. The presenilin 1 mutation (M146V) linked to familial Alzheimer's disease attenuates the neuronal differentiation of Ntera 2 cells. *Biochem Biophsy Res Commun* **244**: 751–755.

Tolar M, Marques MA, Harmony JAK, Crutcher KA. 1997. Neurotoxicity of the 22 kDa thombin-cleavage fragment of apolipoprotein E and related synthetic peptides is receptor-mediated. *J Neurosci* **17**: 5678–5686.

Toleikis PM, Godin DV. 1995. Alteration of antioxidant status in diabetic rats by chronic exposure to psychological stress. *Pharmacol Biochem Behav* **52**: 355–366.

Tomita T, Tokuhiro S, Hashimoto T, Aiba K, Saido TC, Maruyama K, Iwatsubo T. 1998. Molecular dissection of domains in mutant presenilin 2 that mediate overproduction of amyloidogenic forms of amyloid β peptides: Inability of truncated forms of PS2 with familial Alzheimer's disease mutation to increase secretion of Aβ42. *J Biol Chem* **273**: 21153–21160.

Tongiorgi E, Righi M, Cattaneo A. 1997. Activity-dependent dendritic targeting of BDNF and TrkB mRNAs in hippocampal neurons. *J Neurosci* **17**: 9492–9505.

Trapp GA, Miner GD, Zimmerman RL, Mastri AR, Heston LL. 1978. Aluminum levels in brain in Alzheimer's disease. *Biol Psychiat* **13**: 709–718.

Treves T, Korczyn AD, Zilber N, Kahana E, Leibowitz Y, Alter M, Schoenberg BS. 1986. Presenile dementia in Israel. *Arch Neurol* **43**: 26–29.

Tsubokawa H, Oguro K, Robinson HPC, Masuzawa T, Kirino T, Kawai N. 1992. Abnormal Ca^{2+} homeostasis before cell death revealed by whole cell recording of ischemic CA1 hippocampal neurons. *Neuroscience* **49**: 807–817.

Turley SD, Burns DK, Rosenfeld CR, Dietschy JM. 1996. Brain does not utilize low density lipoprotein-cholesterol during fetal and neonatal development in the sheep. *J Lipid Res* **37**: 1953–1961.

Tyrrell J, Cosgrave M, Hawi Z, McPherson J, O'Brien C, McCalvert J, McLaughlin M, Lawlor B, Gill M. 1998. A protective effect of apolipoprotein E ε allele on dementia in Down's syndrome. *Biol Psychiat* **43**: 397–400.

Tysoe C, Robinson D, Brayne C, Dening T, Paykel ES, Huppert FA, Rubinsztein DC. 1996. The tRNA(Gln) 4336 mitochondrial DNA variant is not a high penetrance mutation which predisposes to dementia before the age of 75 years. *J Med Genetics* **33**: 1002–1006.

Ueyama T, Kawai Y, Nemoto K, Sekimoto M, Tone S, Senba E. 1997. Immobilization stress reduced the expression of neurotrophins and their receptors in the rat brain. *Neurosci Res* **28**: 103–110.

Ulrich J. Johannson-Locher G, Seiler WO, Stahelin HB. 1997. Does smoking protect from Alzheimer's disease? Alzheimer type changes in 301 unselected brains from patients with known smoking history. *Acta Neuropathol* **94**: 450–454.

Uno H, Ross T, Else J, Suleman M, Sapolsky R. 1989. Hippocampal damage associated with prolonged and fatal stress primates. *J Neurosci* **9**: 1705–1711.

Urano S, Asai Y, Makabe S, Matsuo M, Izumiyama N, Ohtsubo K, Endo T. 1997. Oxidative injury of synapse and alteration of antioxidative defense systems in rats, and its prevention by vitamin E. *Eur J Biochem* **245**: 64–70.

Urmoneit B, Turner J, Dyrks T. 1998. Cationic lipids (lipofectamine) and disturbance of cellular cholesterol and sphingomyelin distribution modulates γ-secretase activity within amyloid precursor protein *in vitro*. *Prostaglandins Other Lipid Mediat* **55**: 331–343.

Ursini F, Bindoli A. 1987. The role of selenium peroxidases in the protection against oxidative damage of membranes. *Chem Phys Lipids* **44**: 255–276.

Van Cauter E, Leproult R, Kupfer DJ. 1996. Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol levels. *J Clin Endocrinol Metab* **81**: 2468–2473.

van den Berg KJ, Gramsbergen JBP. 1993. Long-term changes in glial fibriallary acidic protein and calcium levels in rat hippocampus after a single systemic dose of kainic acid. *Ann NY Acad Sci* **679**: 394–401.

van den Pol AN, Obrietan K, Chen G. 1996. Excitatory actions of GABA after neuronal trauma. *J Neurosci* **16**: 4283–4292.

Van Duijn CM, Clayton DG, Chandra V, Fratiglioni L, Graves AB, Heyman A, Jorn AF, Kokmen E, Kondo K, Mortimer JA, Rocca WA, Shalat SL, Soininen H, Hofman A. 1994. Interaction between genetic and environmental riks factors for Alzheimer's disease: a reanalysis of case-control studies. EURODEM Risk Factors Research Group. *Genet Epidemiol* **11**: 539–551.

Van Duijn CM, Havekes LM, Van Broeckhoven C, de Knijff P, Hofman A. 1995. Apolipoprotein E genotype and association between smoking and early onset Alzheimer's disease. *Br Med J* **310**: 627–631.

Van Duijn CM, Meijer H, Witteman JCM, Havekes LM, de Knijff P, Van Broeckhoven C, Hofman A. 1996. Estrogen, apolipoprotein E and the risk of Alzheimer's disease. *Neurobiol Aging* **17**(Suppl. 4): S79–S80.

Van Gool WA, Pronker HF, Mirmiran M, Uylings HB. 1987. Effect of housing in an enriched environment on the size of the cerebral cortex in young and old rats. *Exp Neurol* **96**: 225–232.

Van Landeghem GF, Sistrom C, Beckman LE, Adolfsson R, Beckman L. 1998. Transferrin C2, metal binding and Alzheimer's disease. *Neuroreport* **9**: 177–179.

van Leeuwen FW, Burbach JPH, Hol EM. 1998. Mutations in RNA: a first example of molecular misreading in Alzheimer's disease. *Trends Neurosci* **21**: 331–335.

Van Nostrand WE, Melchor JP, Ruffini L. 1998. Pathologic amyloid β-protein cell surface fibril assembly on cultured human cerebrovascular smooth muscle cells. *J Neurochem* **70**: 216–223.

van Rensburg SJ, Daniels WM, van Zyl J, Potocnik FC, van der Walt BJ, Taljaard JJ. 1994. Lipid peroxidation and platelet membrane fluidity — implications for Alzheimer's disease? *Neuroreport* **5**: 2221–2224.

van Rensburg SJ, Carstens ME, Potocnik FC, van der Spuy G, van der Walt BJ, Taljaard JJ. 1995. Transferrin C2 and Alzheimer's disease: another piece of the puzzle found? *Med Hypotheses* **44**: 268–272.

Vatassery GT, Smith WE, Quach HAT, Lai JC. 1995. *In vitro* oxidation of vitamin E, vitamin C, thiols and cholesterol in rat brain mitochondria incubated with free radicals. *Neurochem Int* **26**: 527–535.

Vatassery GT, Quach HT, Smith WE, Ungar F. 1997. Oxidation of cholesterol in synaptosomes and mitochondria isolated from rat brains. *Lipids* **32**: 879–886.

Veenema HC, Spruijt BM, Gispen WH, Van Hooff JARAM. 1997. Aging, dominance history, and social behavior in Java-monkeys (*Macaca fascicularis*). *Neurobiol Aging* **18**: 509–515.

Veinbergs I, Mallory M, Mante M, Rockenstein E, Gilbert JR, Masliah E. 1999. Differential neurotrophic effects of apolipoprotein E in aged transgenic mice. *Neurosci Lett* **265**: 218–222.

Venditti P, Balestrieri M, DiMeo S, DeLeo T. 1997. Effect of thyroid state on lipid peroxidation, antioxidant defences, and susceptibility to oxidative stress in rat tissues. *J Endocrinol* **155**: 151–157.

Vezina J, Tschopp C, Andersen E, Baumann K, Muller K. 1998. Overexpression of a C-terminal fragment of presenilin 1 delays anti-fas induced apoptosis in Jurkat cells. *Neurobiol Aging* **19**(Suppl. 4): S131.

Viani P, Cervato G, Fiorilli A, Cestaro B. 1991. Age-related differences in synaptosomal peroxidative damage and membrane properties. *J Neurochem* **56**: 253–258.

Viitanen M, Guo Z. 1997. Are cognitive function and blood pressure related? *Drugs Aging* **11**: 165–169.

Virgin CE, Sapolsky RM. 1997. Styles of male social behavior and their endocrine correlates among low-ranking baboons. *Am J Primatol* **42**: 25–39.

Visser FE, Aldenkamp AP, van Huffelen AC, Kuilman M, Overweg J, van Wijk J. 1997. Prospective study of the prevalence of Alzheimer-type dementia in institutionalized individuals with Down's syndrome. *Am J Ment Retard* **101**: 400–412.

Vitaliano PP, Russo J, Niaura R. 1995. Plasma lipids and their relationships with psychosocial factors in older adults. *J Gerontol B Psychol Soc Sci* **50**: P18–P24.

Vito P, Ghayur T, D'Adamio L. 1997. Generation of anti-apoptotic presenilin-2 polypeptides by alternative transcription, proteolysis, and caspase-3 cleavage. *J Biol Chem* **272**: 28315–28320.

Volpe BT, Davis HP, Towle A, Dunlap WP. 1992. Loss of hippocampal CA1 pyramidal neurons correlates with impairment in rats with ischemia or neurotoxin lesions. *Behav Neurosci* **106**: 457–464.

Wallace DC, Stugard C, Murdock D, Schurr T, Brown MD. 1997. Ancient mtDNA sequences in the human nuclear genome: a potential source of errors in identifying pathogenic mutations. *Proc Natl Acad Sci USA* **94**: 14900–14905.

Wallin A, Blennow K, Uhlemann C, Langstrom G, Gottfries CG. 1989a. White matter low attenuation on computed tomography in Alzheimer's disease and vascular dementia — diagnostic and pathogenetic aspects. *Acta Neurol Scand* **80**: 518–523.

Wallin A, Gottfries CG, Karlsson I, Svennerholm L. 1989b. Decreased myelin lipids in Alzheimer's disease and vascular dementia. *Acta Neurol Scand* **80**: 319–323.

Walters CE, Austen BM. 1998. Intracellular cholesterol and β-amyloid as factors in Alzheimer's disease. *Neurobiol Aging* **19**(Suppl. 4): S49.

Wang H. 1997. Dementia in old age. In *Dementia*, Welles C (ed.). Davis: Philadelphia; 15–26.

Wang HX, Fratiglioni L, Frisoni GB, Vittanen M, Winblad B. 1999. Smoking and the occurrence of Alzheimer's disease: Cross-sectional and longitudinal data in a population-based study. *Am J Epidemiol* **149**: 640–644.

Wang PN, Wang SJ, Hong CJ, Liu TT, Fuh JL, Chi CW, Liu CY, Liu HC. 1997. Risk factors for Alzheimer's disease: A case-control study. *Neuroepidemiology* **16**: 234–240.

Wang X, Manganaro F, Schipper HM. 1995. A cellular stress model for the sequestration of redox-active glial iron in the aging and degenerating nervous system. *J Neurochem* **64**: 1868–1877.

Wang XS, Gruenstein E. 1997. Rapid elevation of neuronal cytoplasmic calcium by apolipoprotein E peptide. *J Cell Physiol* **173**: 73–83.

Waragai M, Imafuku I, Takeuchi S, Kanazawa I, Oyama F, Udagawa Y, Kawabata M, Okazawa H. 1997. Presenilin I binds to amyloid precursor protein directly. *Biochem Biophys Res Commun* **239**: 480–482.

Warburton DM. 1991. Nicotine as a cognitive enhancer. *Progr Neuro-Psychopharmacol Biol Psychiat* **16**: 181–191.

Ward NI, Mason JA. 1987. Neutron activation analysis techniques for identifying elemental status in Alzheimer's disease. *J Radioanal Nucl Chem* **113**: 515–526.

Warzok RW, Kessler C, Apel G, Schwarz A, Egensperger R, Schreiber D, Herbst EW, Wolf E, Walther R, Walker LC. 1998. Apolipoprotein E4 promotes incipient Alzheimer pathology in the elderly. *Alzheimer Dis Assoc Disord* **12**: 33–39.

Watanabe Y, Gould E, Daniels DC, Cameron H, McEwen BS. 1992. Tianeptine attenuates stress-induced morphological changes in the hippocampus. *Eur J Pharmacol* **222**: 157–162.

Waters SL, Wong JK, Schnellmann RG. 1997. Depletion of endoplasmic reticulum calcium stores protects

against hypoxia- and mitochondrial inhibitor-induced cellular injury and death. *Biochem Biophys Res Commun* **240**: 57–60.

Wei JW, Yang LM, Sun SH, Chiang CL. 1987. Phospholipids and fatty acid profile of brain synaptosomal membrane from normatensive and hypertensive rats. *Int J Biochem* **19**: 1225–1228.

Wei L, Lin SZ, Tajima A, Nakata H, Acuff V, Patlak C, Pettigrew K, Fenstermacher J. 1992. Cerebral glucose utilization and blood flow in adult spontaneously hypertensive rats. *Hypertension* **20**: 501–510.

Weidemann A, Paliga K, Durrwang U, Czech C, Evin G, Masters CL, Beyreuther K. 1997. Formation of stable complexes between two Alzheimer's disease gene products, presenilin-2 and β-amyloid precursor protein. *Nat Med* **3**: 328–332.

Wenstrup D, Ehmann WD, Markesbery WR. 1990. Trace element imbalances in isolated subcellular fractions of Alzheimer's disease brains. *Brain Res* **533**: 125–131.

Wettstein A, Aeppli J, Gautschi K, Peters M. 1991. Failure to find a relationship between mnestic skills of octogenarians and aluminum in drinking water. *Int Arch Occup Environ Hlth* **63**: 97–103.

Whitaker-Azmitia PM, Wingate M, Borella A, Gerlai R, Roder J, Azmitia EC. 1997. Transgenic mice overexpressing the neurotrophic factor S-100β show neuronal cytoskeletal and behavioral signs of altered aging processes: implications for Alzheimer's disease and Down's syndrome. *Brain Res* **776**: 51–60.

White HK, Levin ED. 1999. Four week nicotine skin patch treatment effects on cognitive performance in Alzheimer's disease. *Psychopharmacology* **143**: 158–165.

White LR, Petrovitch H, Ross GW, Masaki K, Izmurlian G, Foley D, Curb JD, Snowdon D, Launer L, Havlik R. 1998. Rates, characteristics, and risk factors for dementia among Japanese-American men in Honolulu — Comparisons with other Japanese- and European-ancestry populations. *Neurobiol Aging* **19**(Suppl. 4): S65.

Whitehouse PJ, Martino AM, Antuono PG, Lowenstein PR, Coyle JT, Price DL, Kellar KJ. 1986. Nicotinic acetylcholine binding sites in Alzheimer's disease. *Brain Res* **371**: 146–151.

Whybrow PC, Prange AJ, Treadway CR. 1969. Mental changes accompanying thyroid gland dysfunction. *Arch Gen Psychiat* **20**: 48–63.

Widmaier EP, Margenthaler J, Sarel I. 1995. Regulation of pituitary-adrenocortical activity by free fatty acids *in vivo* and *in vitro*. *Prostaglandins Leukotrienes Essential Fatty Acids* **52**: 179–183.

Wilkie F, Eisdorfer C. 1971. Intelligence and blood pressure in the aged. *Science* **172**: 959–962.

Williams L, Garton S, Frederiksen K, Richards S-J. 1998. Immortalised Trisomy 16 cell lines demonstrate aberrant amyloid processing and an abnormal cytoskeleton. *Neurobiol Aging* **19**(Suppl. 4): S200.

Winokur A, Maislin G, Phillips JL, Amsterdam JD. 1988. Insulin resistance after oral glucose tolerance testing in patients with major depression. *Am J Psychiat* **145**: 325–330.

Wisniewski HM, Rabe A. 1986. Discrepancy between Alzheimer-type neuropathology and dementia in persons with Down's syndrome. *Ann NY Acad Sci* **477**: 247–259.

Wisniewski KE, Laure-Kamionowska M, Wisniewski HM. 1984. Evidence of arrest of neurogenesis and synaptogenesis in brains of patients with Down's syndrome. *N Engl J Med* **311**: 1187–1188.

Wisniewski HM, Frackowiak J, Mazur-Kolecka B. 1995. *In vitro* production of β-amyloid in smooth muscle cells isolated from amyloid angiopathy-affected vessels. *Neurosci Lett* **183**: 120–123.

Wisniewski HM, Vorbrodt AW, Wegiel J. 1997. Amyloid angiopathy and blood–brain barrier changes in Alzheimer's disease. *Ann NY Acad Sci* **826**: 161–172.

Wisniewski T, Castano EMN, Golabek A, Vogel T, Frangione B. 1994. Acceleration of Alzheimer's fibril formation by apolipoprotein E *in vitro*. *Am J Pathol* **145**: 1030–1035.

Wolkowitz OM. 1994. Prospective controlled studies of the behavioral and biological effects of exogenous corticosteroids. *Psychoneuroendocrinology* **19**: 233–255.

Wolozin B, Iwasaki K, Vito P, Ganjei JK, Lacana E, Sunderland T, Zhao BY, Kusiak JW, Wasco V, D'Adamio L. 1996. participation of presenilin-2 in apoptosis — enhanced basal activity conferred by an Alzheimer mutation. *Science* **274**: 1710–1713.

Wong A, Cortopassi G. 1997. mtDNA mutations confer cellular sensitivity to oxidant stress that is partially rescued by calcium depletion and cyclosporin A. *Biochem Biophys Res Commun* **239**: 139–145.

Wonnacott S. 1990. The paradox of nicotinic acetylcholine receptor upregulation by nicotine. *Trends Pharmacol Sci* **11**: 216–219.

Wood DJ, Cooper C, Stevens J, Edwardson J. 1988. Bone mass and dementia in hip fracture patients from areas with different aluminium concentrations in water supplies. *Age Ageing* **17**: 415–419.

Wood ER, Mumby DG, Pinel JPJ, Phillips AG. 1993. Imparied object recognition memory in rats following ischemia-induced damage to the hippocampus. *Behav Neurosci* **107**: 51–62.

Wood WG, Igbavboa U, Rao AM, Schroeder F, Avdulov NA. 1995. Cholesterol oxidation reduces $Ca^{2+}+Mg^{2+}$-ATPase activity, interdigitation, and increases fluidity of brain synaptic plasma membranes **683**: 36–42.

Wood WG, Avdulov NA, Chochina SV, Igbavboa I. 1998. Aβ-peptide$_{1-40}$ induced increased in neuronal membrane fluidity is dependent on brain area and lipid composition. *Neurobiol Aging* **19**(Suppl. 4): S48.

Woods AG, Kurlawalla MA, Yong AP, Hess US, Gall CM. 1998. Endogenous glucocorticoids suppress microgilal trophic responses to denervation in aged rat hippocampus. *Soc Neurosci Abstr* **24**: 1973.

Wragg MA, Talbot CJ, Morris JC, Lendon CL, Goate AM. 1995. No association found between Alzheimer's disease and a mitochondrial tRNA glutamine gene variant. *Neurosci Lett* **201**: 107–110.

Wright SC, Zhong J, Zheng H, Larrick JW. 1993. Nicotine inhibition of apoptosis suggests a role in tumor promotion. *FASEB J* **7**: 1045.

Wustenberg F, Berlin K, Scharnagl H, Marz W, Ohm TG, Muller W. 1997. Complexes of APOE isoforms and β-amyloid peptides elevate intracellular calcium levels differentially. In *Alzheimer's Disease: Biology, Diagnosis and Therapeutics*, Iqbal K, Winblad B, Nishimura T, Takeda M, Wisniewski HM (eds). John Wiley: Chichester; 383–387.

Xia W, Zhang J, Perez R, Koo EH, Selkoe DJ. 1997. Interaction between amyloid precursor protein and prsenilins in mammalian cells: implications for the pathogenesis of Alzheimer's disease. *Proc Natl Acad Sci USA* **94**: 8208–8213.

Xia WM, Zhang JM, Ostaszewski BL, Kimberly WT, Seubert P, Koo EH, Shen J, Selkoe DJ. 1998. Presenilin 1 regulates the processing of β-amyloid precursor protein C-terminal fragments and the generation of amyloid β-protein in endoplasmic reticulum and Golgi. *Biochemistry* **37**: 16465–16471.

Xie HG, Wang LN, Wang ZhF, Wang XH. 1998. A preliminary epidemiological study of the dementias in male veterans. *Neurobiol Aging* **19**(Suppl. 4): S27.

Xiong Y, Gu Q, Peterson PL, Muizelaar JP, Lee CP. 1997. Mitochondrial dysfunction and calcium pertubation induced by traumatic brain injury. *J Neurotrauma* **14**: 23–34.

Yallampalli S, Micci MA, Taglialatela G. 1998. Ascorbic acid prevents β-amyloid-induced intracellulr calcium increase in cell death in PC12 cells. *Neurosci Lett* **251**: 105–108.

Yamaji S, Ishii K, Sasaki M, Imamura T, Kitagaki H, Sakamoto S, Mori E. 1997. Changes in cerebral blood flow and oxygen metabolism related to magnetic resonance imaging white matter hyperintensities in Alzheimer's disease. *J Nucl Med* **38**: 1471–1474.

Yamashita H, Nakamura S. 1996. Nicotine rescues PC12 cells from death induced by nerve growth factor deprivation. *Neurosci Lett* **213**: 145–147.

Yamatsuji T, Matsui T, Okamoto T, Komatsuzaki K, Takeda S, Fukumoto H, Iwatsubo T, Suzuki N, Asamiodaka A, Ireland S, Kinane TB, Giambarella U, Nishimoto I. 1996. G-protein-mediated neuronal DNA fragmentation induced by familial Alzheimer's disease-associated mutants of APP. *Science* **272**: 1349–1352.

Yamikami I, McIntosh TK. 1989. Effects of traumatic brain injury on regional cerebral blood flow in rats as measured with radiolabeled microspheres. *J Cerb Blood Flow Metab* **9**: 117–124.

Yang L, Benardo LS. 1997. Epileptogenesis following neocortical trauma from two sources of disinhibition. *J Neurophysiol* **78**: 2804–2810.

Yang X-H, Buccafusco JT. 1994. Comparison of the ability of direct and indirect-acting nicotinic agonists to induce nicotinic receptor up-regulation in rat cerebral cortex. *Drug Dev Res* **31**: 95–101.

Yankner BA, Wong C, Fernandez G, Yuan M, Mori H, Busciglio J. 1998. Altered metabolism of the amyloid precursor protein and neurodegeneration in Down's syndrome. *Neurobiol Aging* **19**(Suppl. 4): S2.

Yasuda M, Mori E, Kitagaki H, Yamashita H, Hirono N, Shimada K, Maeda K, Tanaka C. 1998. Apolipoprotein E ε4 allele and whole brain atrophy in late-onset Alzheimer's disease. *Am J Psychiat* **155**: 779–784.

Ye P, Umayahara Y, Ritter D, Bunting T, Auman H, Rotwein P, D'Ercole AJ. 1997. Regulation of insulin-like growth factor I (IGF-I) gene expression in brain of transgenic mice expressing an IGF-I-luciferase fusion gene. *Endocrinology* **138**: 5466–5475.

Yoshikawa K, Aizawa T, Hayashi Y. 1992. Degeneration *in vitro* of post-mitotic neurons overexpressing the Alzheimer amyloid protein precursor. *Nature* **359**: 64–67.

Yoshitake T, Kiyohara Y, Kato I, Ohmura T, Iwamoto H, Nakayama K, Ohmori S, Nomiyama K, Kawano H, Ueda K, Sueshi K, Tsuneyoshi M, Fujishima M. 1995. Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama Study. *Neurology* **45**: 1161–1168.

Yumoto S, Horino Y, Mokuno Y, Kakimi S, Fujii K. 1996. Microprobe pixe analysis of aluminum in the brains of patients with Alzheimer's disease. *Nucl Instrum Meth Phys Res Sect B — Beam Interactions Mater Atoms* **109**: 362–367.

Zamani MR, Allen YS, Owen GP, Gray JA. 1997. Nicotine modulates the neurotoxic effect of β-amyloid protein(25–35) in hippocampal cultures. *Neuroreport* **8**: 513–517.

Zareparsi S, Kaye J, Camicioli R, Grimslid H, Oken B, Litt M, Nutt J, Bird T, Schellenberg G, Payami H. 1997. Modulation of the age at onset of Parkinson's disease by apolipoprotein E genotypes. *Ann Neurol* **42**: 655–658.

Zarow C, Barron E, Chui HC, Perlmutter LS. 1997. Vascular basement membrane pathology and Alzheimer's disease. *Ann NY Acad Sci* **826**: 147–160.

Zekraoui L, Lagarde JP, Raisonnier A, Gerard N, Aouizerate A, Lucotte G. 1997. High frequency of the apolipoprotein E ε4 allele in African pygmies and most of the African populations in sub-Saharan Africa. *Hum Biol* **69**: 575–581.

Zerbib R, Laborit H. 1990. Chronic stress and memory: implication of the central cholinergic system. *Pharmacol Biochem Behav* **36**: 897–900.

Zhang S, Wong WW, Hachey DL, Pond WG, Klein PD. 1994. Dietary cholesterol inhibits whole-body but not cerebrum cholesterol synthesis in young pigs. *J Nutrit* **124**: 717–725.

Zhou D, Kusnecov AW, Shurin MR, DePaoli M, Rabin BS. 1993. Exposure to physical and psychological stressors elevates plasma interleukin-6, relationship to the activation of hypothalamic–pituitary–adrenal axis. *Endocrinology* **133**: 2523–2530.

Zhou Y, Richardson JS. 1996. Cholesterol protects PC12 cells from β-amyloid induced calcium disordering and cytotoxicity. *Neuroreport* **7**: 2487–2490.

Zhou Y, Elkins PD, Howell LA, Ryan DH, Harris RBS. 1998. Apolipoprotein-E deficiency results in an altered stress responsiveness in addition to an impaired spatial memory in young mice. *Brain Res* **788**: 151–159.

Zhou Y, Cheshire A, Howel LA, Ryan DH, Harris RBS. 1999. Neuroautoantibody immunoreactivity in relation to aging and stress in apolipoprotein E-deficient mice. *Brain Res Bull* **49**: 173–179.

Zhou Z, Smith JD, Greengard P, Gandy S. 1996. Alzheimer amyloid-β peptide forms denaturant-resistant complex with type E3 but not type E4 isoform of native apolipoprotein E. *Mol Med* **2**: 175–180.

Zhu L, Fratiglioni L, Guo ZC, Aguero-Torres H, Winblad B, Viitanen M. 1998a. Association of stroke with dementia, cognitive impairment, and functional disability in the very old: A population-based study. *Stroke* **29**: 2094–2099.

Zhu L, Viitanen M, Guo ZC, Winblad B, Fratiglioni L. 1998b. Blood pressure reduction, cardiovascular diseases, and cognitive decline in the mini-mental state examination in a community population of normal very old people: A three-year follow-up. *J Clin Epidemiol* **51**: 385–391.

Zoli M, Ferraguti F, Gustafsson JA, Toffano G, Fuxe K, Agnati LF. 1991. Selective reduction of glucocorticoid receptor immunoreactivity in the hippocampal formation and central amygdaloid nucleus of the aged rat. *Brain Res* **545**: 199–207.

Zubenko GS, Cohen BM, Growdon J, Corkin S. 1984. Cell membrane abnormality in Alzheimer's disease. *Lancet* **2**: 235.

Zubenko GS, Moossy J, Claassen D, Martinez AJ, Rao GR. 1990. Brain regional analysis of NADH-cytochrome C reductase activity in Alzheimer's disease. *J Neuropathol Exp Neurol* **49**: 206–214.

Zubenko GS, Hughes HB, Stiffler JS, Hurtt MR, Kaplan BB. 1998a. A genome survey for novel Alzheimer's disease risk loci: Results at 10-cM resolution. *Genomics* **50**: 121–128.

Zubenko GS, Stiffler JS, Hughes HB, Hurtt MR, Kaplan BB. 1998b. Initial results of a genome survey for novel Alzheimer's disease risk genes: Association with a locus on the X chromosome. *Am J Med Genetics* **81**: 196–205.

