# Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics

**Jack C de la Torre**

**The cause of Alzheimer's disease (AD) is unknown. This gap in knowledge has created a stumbling block in the search for a genuinely effective treatment or cure for this dementia. This article summarises the arguments for a causal role for either amyloid deposition or cerebrovascular pathology as the primary trigger in the development of non-genetic AD. A bare-bones survey of the published research reveals no compelling evidence that amyloid deposition is neurotoxic in human beings or that it results in neurodegenerative changes involving synaptic, metabolic, or neuronal loss in human or transgenic-mouse brains. By contrast, the data supporting AD as a primary vascular disorder are more convincing. Findings suggesting a vascular cause of AD come from epidemiological, neuroimaging, pathological, pharmacotherapeutic, and clinical studies. The consensus of these studies indicates that chronic brain hypoperfusion is linked to AD risk factors, AD preclinical detection and pharmacotherapeutic action of AD symptoms.**

*Lancet Neurol* 2004; **3:** 184–90

One of the major puzzles in Alzheimer's disease (AD) research is what causes the disorder. The answer is extremely important because the main stumbling block in the search for a cure of AD is that its pathogenesis is a mystery wrapped in controversy. Knowing the cause of AD would have a major effect on clinical practice and the delivery of public health services. More specifically, it would likely lead to the development of a highly effective treatment or cure for AD. With 21 million people expected to have AD by the year 2010 in countries that keep such a census, a treatment would likely be worth over US$5 billion a year in sales and would displace the minimally effective remedies available.

Although many theories on the cause of AD have surfaced over the past quarter of a century, few have survived the test of time. The exception has been the "amyloid hypothesis", first proposed from research conducted in the middle of the 1980s showing that senile plaques found in AD brain tissue were composed mainly of a sticky amyloid-β peptide (Aβ).[1] For over a decade, the amyloid hypothesis has so influenced and guided research in AD that many workers regard it as the gold standard of scientific investigation.

This article will present the arguments that support either amyloid deposition or cerebral hypoperfusion as the primary pathway leading to non-genetic AD (figure). Although AD expression may be triggered by reduced cerebral perfusion before clinical symptoms of AD develop in carriers of the presenilin-1 mutation, I will not review the genetic features of AD.[2]

This paper will also summarise why, despite the thousands of "brilliant" minds involved in the research, neither the cause of nor the cure for AD have been found. Finally, I will discuss efforts to match "fact to theory" by borrowing from Socratic dialectics and from the laws of probability in order to provide a working explanation of the AD puzzle.

## Is AD neurodegenerative?

The notion that AD is a neurodegenerative disorder may have begun with a paper by Roth in 1955,[3] who observed that AD results from a neurodegenerative process and can be distinguished from vascular dementia by the different mental changes caused by each. Since then, the present criteria for differentiating AD from vascular dementia have largely been based on "expert opinion" rather than a critical review of the scientific evidence.[4] Thus, according to the authoritative *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM IV), the presence of cerebrovascular disease in a demented individual excludes the diagnosis of AD and, instead, the disorder is classified as a vascular dementia.[5]

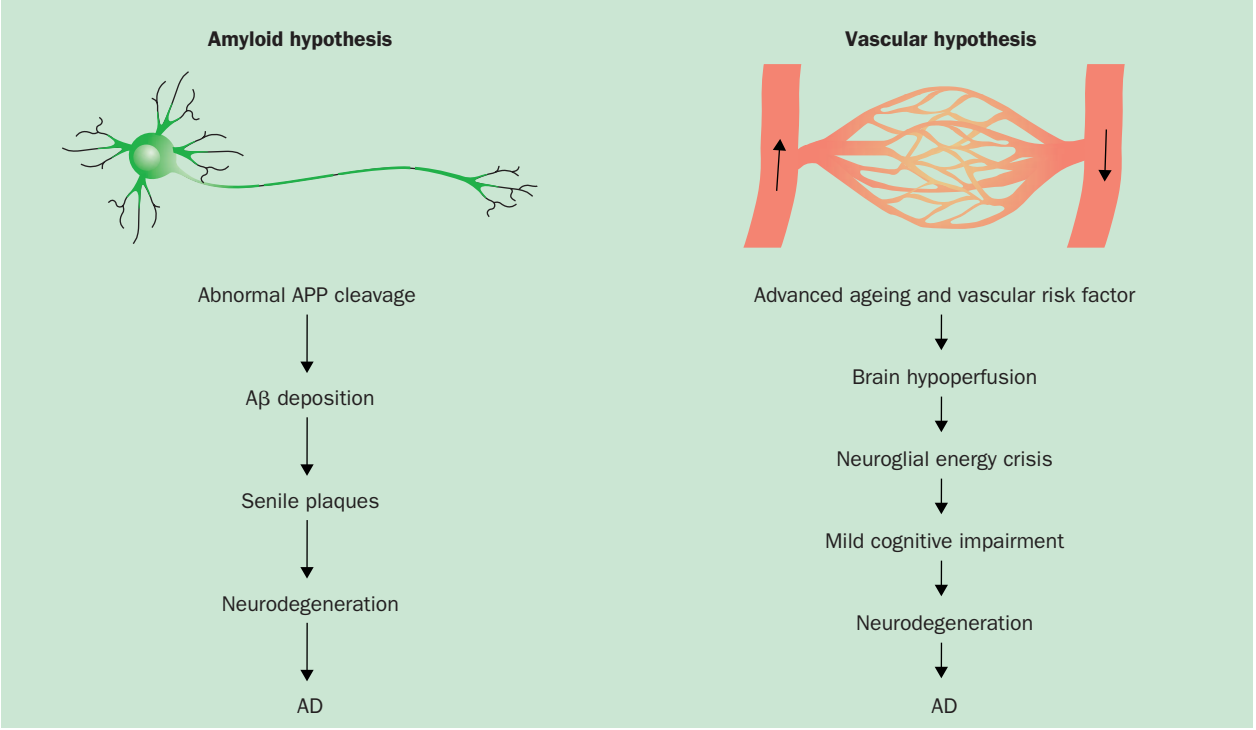
In 1991, it was proposed that deposition of fibrillar and insoluble Aβ causes neurodegeneration in AD.[6] Aβ is a 39–42 amino-acid-residue fragment derived from proteolysis of the amyloid precursor protein (APP) and it is the major component of senile plaques.[6,7] According to the amyloid hypothesis, deposition and accumulation of Aβ in the brain is the primary factor driving AD pathogenesis.[6] The pathological process involving the formation of neurofibrillary tangles containing tau protein, is thought to begin with an imbalance between production and clearance of Aβ.[8]

Four major observations[8] are used to support the amyloid hypothesis as the direct initiator of AD pathogenesis: neurofibrillary tangles that are associated with neurodegeneration are insufficient to induce amyloid plaques in AD; transgenic mice that overexpress mutant human APP and mutant human tau have more tau-positive tangles but a normal density of amyloid plaques; the human *APOE* locus seems to involve Aβ metabolism; Aβ catabolism and clearance may be a risk factor for late-onset AD.

The idea that AD is caused by the formation of senile plaques, which subsequently lead to the formation of neurofibrillary tangles, has been criticised not only for the lack of coherent evidence[9–12] but also for its failure to provide an effective treatment for AD.[13,14]

JCT is at the Institute of Pathology, Case Western Reserve University, Cleveland, Ohio, USA.

**Correspondence:** Dr Jack C de la Torre, Institute of Pathology, Case Western Reserve University, Cleveland, Ohio 44106, USA. Tel +1 (760) 743 7441; fax +1 (760) 747 3313; email jdelator@nctimes.net




*The presumed pathological pathway leading to the development of Alzheimer's disease according to the amyloid[8] or vascular hypothesis.[76]*

The two main flaws of the amyloid hypothesis are that Aβ deposition has never been found to be neurotoxic in vivo, and that because there is general agreement that senile plaques are the products of sick neurons, they cannot be the cause of neuronal sickness, because it is axiomatic that a product is the result not the cause of some activity.[13]

Other difficulties with the amyloid hypothesis have been reported. These can be summarised as follows: (1) Aβ deposition in the brain does not relate with dementia severity.[15] (2) Many patients without dementia have the same density of senile plaques as patients with AD.[16] (3) Amyloid deposition is not the earliest neuropathological event observed in those afflicted with the disease.[17,18] (4) Many cognitively healthy elderly people have abundant senile plaques in their brains but no signs of AD.[19] (5) Amyloid deposition in the brain does not correlate to neuronal, metabolic, or synaptic loss.[15,20,21] (6) Amyloid plaques can be found in other dementias including vascular dementia.[22,23] (7) Experiments with transgenic mice that produce Aβ deposits in the brain show, as in human beings, no relation between such deposits and neuronal, metabolic, or synaptic loss.[22–26] (8) The same transgenic mice also show cognitive loss before Aβ is deposited in the brain.[24] (9) Memory loss is independent of Aβ overexpression in transgenic mice.[26] (10) Transgenic mice overexpressing the 695 amino-acid residue isoform of human APP show low glucose metabolism and gliosis in the entorhinal cortex, hippocampus, and neocortex in the absence of Aβ deposits,[27] which suggests a neuronal-energy deficit precedes amyloid deposition. (11) In mice transgenic for APP and presenilin 1 with memory-impairment, vaccinations against Aβ over 8 weeks do not improve cognition.[28]

To skate around these difficulties, proponents of the original amyloid hypothesis recently suggested that soluble oligomers of $A\beta_{1-42}$ and not its insoluble amyloid fibrils or monomers (as previously suggested)[29] are the cause of synaptic dysfunction in AD and in animal models that mimic AD.[8] This view, however, has been challenged because there are no data that soluble oligomers of $A\beta_{1-42}$ cause either cell death, neuronal dysfunction, or cognitive loss in vivo.[30] Moreover, if the suggestion that AD is caused by soluble oligomers of $A\beta_{1-42}$ is correct, vaccination to dissolve fibrillar plaques (as was the aim in trials of AN1792 immunisation) would likely speed up the pathological progress of AD in the vaccinated patients.[30] The vaccine trial, however, was suspended when it caused meningoencephalitis in 18 of the patients given this treatment.[31]

Whether a product of APP proteolysis is toxic or even harmful to neurons and not a protective neuronal response to stave off death is now the subject of considerable debate.[32,33] For example, a recent article reports that the production of Aβ plays a crucial part in maintaining the survival of rat-brain neurons.[34] This topic, including the potential of Aβ to bind neurotoxic molecules as a response to neuronal injury, has been comprehensively reviewed.[35]

Many transgenic mouse lines have consistently disproved the amyloid hypothesis, a verdict ignored by supporters of this doctrine.[12,22–28] Amyloid proponents, however, select specific data from transgenic mice research to support the amyloid hypothesis while ignoring the bulk of evidence that discredits it.

Although the amyloid hypothesis has been accepted by many as a statement of fact and used as a rationale to design treatments for AD, there is little evidence to support its validity and ample evidence to question it.

## Is AD a vascular disorder?

There is now substantial and growing evidence from studies of epidemiology, pharmacology, neuroimaging, clinical medicine, microscopic anatomy, and cellular-molecular biology to suggest that sporadic AD is a vascular disorder caused by impaired cerebral perfusion. This proposal was first submitted 10 years ago.[36]

Because much of the data in support of a vascular aetiology for AD has been reported elsewhere,[37–40] I will focus on three areas: epidemiology, pharmacotherapy, and neuroimaging.

### *Epidemiological studies*

Several dozen risk factors for AD have been compiled and reported from different epidemiological studies, including The Rotterdam Study, the Kungsholmen project, EURODEM, FINMONICA, and the Honolulu–Asia study (panel).[41–44] These risk factors may be just the tip of the iceberg, but their consensus already provides a powerful argument for impaired cerebral perfusion as the primary trigger in the development of AD. All these risk factors are vascular-related and all impair or reduce cerebral perfusion (panel).

**Reported risk factors for AD**

**Heart-related risk factors**
Congestive heart failure
Cardiac arrhythmia
Hypertension
Hypotension
Thrombotic episodes
High concentrations of homocysteine in the serum
Atrial fibrillation
Presence of *APOE* ε4 allele
Atherosclerosis

**Peripheral risk factors**
Smoking
Alcoholism
High serum cholesterol
High intake saturated fat
Diabetes mellitus
Haemorheological abnormalities
High cholesterol concentrations in the plasma

**Brain-related risk factors**
Ageing
Ischaemic stroke
Silent stroke
Head injury
Transient ischaemic attack
Menopause
Migraine
Lower education
Haemodynamic abnormalities
Depression

For example, the authors of the Rotterdam Study concluded from their data—on over 7000 demented and non-demented elderly people—that "vascular risk factors, and indicators of vascular disease, particularly in elderly patients, have an established association with AD".[44]

Nearly all of the risk factors (panel) are present not only at the onset of AD but also decades before any loss of cognitive function develops.

Three of the most important vascular-related risk factors for AD are stroke, cardiac disease, and atherosclerosis. It is not surprising that these three disorders are linked by haemodynamic and blood-pressure abnormalities because their source is the heart and their outcome involves brain ischaemia or hypoxia and vessel damage.

#### *Stroke*

Stroke has been shown to be closely associated with AD in many studies.[37–41,45,46] Post-mortem studies of patients with AD show that their brains contain amyloid angiopathy and microvascular degeneration affecting the capillary endothelium, vascular smooth muscle cells, and basal lamina.[47]

Other post-mortem studies in elderly Japanese-American males reveal that microvascular lesions were about as common as classic AD markers (senile plaques and neurofibrillary tangles).[48] The question arises as to whether AD stimulates stroke and cerebrovascular pathology or the other way around. There is no evidence for the former possibility but there is some for the latter.

For instance, cerebrovascular pathology—including stroke—seems to play an important part in the eventual development of AD clinical symptoms.[46,49–51] Moreover, a significant association has been shown between cortical microinfarcts and AD (32·4% in patients *vs* 2·5% in controls).[52] The microinfarcts were restricted to the watershed cortical zones suggesting that disturbed haemodynamic factors have roles in the genesis of cortical watershed microinfarcts that can precede AD symptoms.[52]

In a recent study of 1015 people, who were age 60–90 years, without dementia at baseline,[53] the presence of silent (asymptomatic) stroke more than doubled the risk of AD. In patients with subcortical lacunar infarction (typical of silent stroke) studied with PET and MRI, cerebral glucose hypometabolism was related to the degree of cognitive impairment, which indicated that hypometabolism resulting from regional hypoperfusion was a stronger correlate of cognitive impairment than cerebral morphological changes such as atrophy of the hippocampus.[54] Silent stroke is commonly associated with hypertension,[55] atrial fibrillation,[56] and ageing,[57] all risk factors for AD.

In a post-mortem study of 102 elderly nuns, atherosclerosis of the circle of Willis was present in every brain and was strongly associated with lacunar and large brain infarcts, which suggests that ischaemic stroke may have been a main cause of AD.[46]

Because about 25 million people worldwide have silent and symptomatic stroke annually,[58] this disease will undoubtedly continue to provide a critical pool of AD

candidates in the near future. Aggressive therapy should be considered in elderly individuals who show signs of cerebrovascular disease.

*Cardiac disease*

Myocardial infarction,[44,59] atrial fibrillation,[60] and congestive heart failure[61] are risk factors for AD. Consequently, the neuropathological link between cardiac abnormalities and their satellite off-shoots, such as vessel plaque formation, hypertension, and presence of the *APOE* ϵ4 gene,[62] seem to form a vascular complex that may target AD via specific cardiogenic pathways.

A likely critical predisposing factor for AD is cardiac surgery, specifically coronary artery bypass graft (CABG).[63] Studies of patients given CABG show that nearly 50% have cognitive impairment immediately after surgery.[63] Most of these patients continue their cognitive dysfunction 5 years after surgery. This finding implies that permanent brain lesions may already exist, thus placing these patients at a greater risk of dementia (AD, vascular dementia, or mixed dementia). With more than 150 000 new patients undergoing CABG surgery every year in the USA alone,[64] the problem warrants considerable efforts to prevent and identify patients at risk for postoperative cognitive dysfunction.[65] Prospective population studies could determine whether CABG is a major promoter of AD or other dementias.

Since 20% of cardiac output goes to the brain, and 80% of carotid artery flow goes to the ipsilateral middle cerebral artery, it is no surprise that vascular lesions of the brain are commonly associated with cardiac disease and carotid artery occlusion, both of which are risk factors for AD (panel).[37–46,52]

One of the main complications of sustained systemic hypertension is small vessel atherosclerosis of the intracranial vasculature, particularly of vessels that come off their parent vessels at right angles. These include the lenticulostriate vessels (which supply the basal ganglia and thalamus), midline pontine perforators (the pons), and deep penetrating cerebellar vessels (the cerebellar white matter). These vascular branches are commonly involved in lacunar infarcts occurring mostly in the basal ganglia and thalamus (70%), pons (15%), and cerebellar white matter (15%). Such infarcts can precipitate the development of AD.[46,53]

*Atherosclerosis*

The risk of either AD or vascular dementia was three times higher in people with severe atherosclerosis.[66] In a 6-year follow-up study involving 1270 dementia-free elderly people, severe arterial stiffness and atherosclerosis resulting in high pulse pressure (high systolic and low diastolic pressures) was found to significantly increase the incidence of AD or vascular dementia.[67] These findings indicate that arterial compliance, left ventricular ejection rate, and stroke volumes are important determinants of dementia in elderly people.

Blood vessels with many atherosclerotic plaques generally have endothelial and perivascular cell damage,[68] a disorder that can lead to dysregulation of blood flow by blocking endothelial-derived nitric-oxide release and by physically diminishing blood volume in relation to luminal stenosis.[69–70] Apart from the many negative effects that can occur from endothelial nitric oxide dysfunction after chronic brain ischaemia, the loss of spatial memory and the accumulation of soluble $A\beta_{40}$ in rat hippocampus[71] could be key outcomes of sustained carotid artery occlusion.

These findings make sense in the light of other data showing the effects of chronic cerebral hypoperfusion on human cognition. Studies in patients with carotid artery stenosis of long duration and in those who have had carotid endarterectomy to improve blood flow are controversial because surgery can generate cerebral microemboli even when carotid artery stenosis is reversed.[72] However, when global brain hypoperfusion after carotid endarterectomy is reversed and no microembolic events are recorded, cognitive ability generally improves.[73] Conversely, if microemboli are generated or the hypoperfused state is not corrected after carotid endarterectomy, cognitive ability is unimproved in many cases.[70,74]

Because atherosclerosis is generally accepted to take decades to develop and manifest itself in many cases, it is reasonable to assume that occlusive blood flow to the brain from stenosed or blocked carotid arteries leading to cognitive dysfunction is an event that likely precedes dementia symptoms by many years.[66] If this is true, intervention to prevent or reduce atherosclerosis could lessen the prevalence of AD.

It should be pointed out that stroke, cardiac disease, and atherosclerosis are also risk factors for vascular dementia, as are most other AD risk factors. [13,41–44,57,60,66] Because AD and vascular dementia also share similar pathological hallmarks, clinical symptoms, psychometric testing results, and interchangeable treatment potential,[14,23,47,55,60] these two disorders should no longer be thought of as dichotomous but as possible extensions of one dementia with a common basis.

The epidemiological studies reviewed show that an AD risk factor is most likely to be vascular-related,[41–44] that vascular-related risk factors reduce or impair cerebral blood flow (which in the presence of advanced ageing creates a "double burden" for cerebral perfusion),[13,14,75,76] and that the association between vascular-related risk factors and the potential development of AD is unlikely to be coincidental. Moreover, these epidemiological findings indicate that—despite the discrete pathology involved in many of these vascular-related risk factors and their divergent clinical course and outcome—all reduce or impair cerebral perfusion. Elementary statistical analysis shows that the common interconnecting feature of practically all AD risk factors is cerebral hypoperfusion. These risk factors are not directly related to the production of Aβ in AD. Moreover, there seems to be no other common feature that connects these risk factors more fittingly than the link to vascular pathology. Not only are many of the risk factors for AD also risk factors for vascular dementia, but also the two disorders share many clinicopathological similarities.[42,43,47,75–77] The overlap between vascular dementia and AD has recently been discussed at length.[38–40]

If only epidemiological evidence were available, it would represent a compelling argument for a vascular pathogenesis for AD. But there is more.

## Pharmacotherapy

For nearly a quarter of a century, a mostly useless cornucopia of pharmacological products has been given to patients with AD in an effort to reduce, reverse, abolish, or slow down the progressive cognitive decline. Only three drugs are available in the USA for prescriptive use in AD: tacrine (Cognex), donepezil (Aricept), and rivastigmine tartrate (Excelon). All three slow the synaptic breakdown of acetylcholine, one of many neurotransmitters important in memory and learning. A fourth drug, galantamine hydrobromide (Reminyl) targets both AD and mixed dementia (ie, either vascular dementia or AD complicated by cerebrovascular pathology).

These treatments, at best, provide only modest symptomatic control at the early stages of AD and offer little to no benefit at the later stages of the disease. An expected US$5 billion market has spurred the introduction of other near-worthless remedies. Initially promising therapies such as non-steroidal anti-inflammatory agents (NSAIDs), ginkgo biloba, oestrogen, vitamin E, and memantine, have not lived up to expectations.[76–80]

Nonetheless, all drugs tried so far for AD are able to increase or improve cerebral perfusion but only transiently and very modestly.[81] It is possibly this effect on cerebral perfusion that makes some of these medicines "somewhat useful" for a short duration. Transient symptomatic improvements, or even a low risk of AD, have been reported in elderly people engaging in certain mental and physical activities—the "use it or lose it" phenomenon. Consequently, this outcome could be because mental activity can stimulate cerebral blood flow[82] and cardiac exercise can reduce the cholesterol build-up in major arteries that can diminish cerebral perfusion and promote hypertension.[83] However, no drug or mental–physical activity tried so far has been able to reduce, reverse or abolish the progressive pathology of this dementia. This grim conclusion suggests that a "magic bullet" is unlikely to control or reverse AD pathology.

## New treatment opportunities

I have reviewed elsewhere other treatment possiblities, including techniques that can create neoangiogenesis and vasculogenesis with growth factors, gene manipulation, stem cells, surgery, and endothelial-cell seeding.[13] These experimental approaches have not yet been tried in AD but their aim would be to improve cerebral perfusion to a level that is both sustainable and sufficient to rescue energy-starved dysfunctional neurons or protect them from further damage.[84] To this end, I have proposed that one of the primary pathological events involved in the development of AD begins as an endotheliopathy from damage to endothelial cells after chronic brain hypoperfusion.[14,36,69,71,75] Endothelial cells form a one-cell thick lining of all blood vessels in the body, including the brain. Paradoxically these cells normally form a nonadhesive surface to leucocytes and monocytes, but when damaged they may recruit these same cells in an attempt to use them for repair purposes. Cerebral endothelial-cell injury has been reported in several animal models of cognitive impairment with chronic brain hypoperfusion[85–87] and is generally present in brain capillaries early in AD.[88–90]

One of the more promising lines of research into the restoration of cerebral blood flow homoeostasis, and which may have therapeutic application to AD, involves the use of endothelial progenitor cells. These cells can be isolated from circulating mononuclear cells and bone marrow. When these cells are injected into animal models of ischaemia, they are quickly incorporated by the ischaemic sites and create neovascularisation.[91–95] Furthermore, there is evidence that tissue ischaemia mobilises endothelial progenitor cells from bone marrow into the circulation as a repair response by increasing their incorporation at sites of neovascularisation.[91,96] In one study,[97] endothelial progenitor cells were assimilated into cardiac capillaries 4 weeks after myocardial infarction. Histology revealed that these cells formed neovascularised areas at the border of the infarct.[97]

More studies are needed to examine the possibility that after cerebromicrovascular endothelial-cell injury, AD pathology may accelerate if the numbers of circulating progenitor cells become suboptimal.

## Neuroimaging studies

Neuroimaging has become an important tool in the preclinical detection and in monitoring the development and decline in AD. Neuroimaging techniques that provide direct information on brain function in AD use scans that record direct regional CBF patterns using single-photon emission CT (SPECT) and indirectly from uptake of injected fluorine-18-labelled fluorodeoxyglucose with PET.

Recent findings suggest that a transition stage before AD begins with mild cognitive impairment, defined as memory dysfunction with preservation of other cognitive and functional activities.[98] Patients with mild cognitive impairment do not generally meet the criteria set by the Alzheimer's Disease and Related Disorders Association (ADRDA) for possible or probable diagnosis of AD. However, about 50% of people with mild cognitive impairment develop AD, and identification of these patients allows preventive interventions to be used to delay complete cognitive meltdown.[98]

One technique that enables preclinical detection of AD during mild cognitive impairment is based on analysis of cerebral hypoperfusion patterns on SPECT in people who have problems of memory. In one study, patients with memory complaints not meeting the ADRDA criteria for AD and have no apparent tissue damage to their brains, had their regional cerebral blood flow measured with SPECT and were separated into two groups.[81] Most of those with significant hypoperfusion of the hippocampal-amygdaloid complex (areas linked to memory function) converted to AD within 3 years, whereas patients with normal cerebral perfusion in these and other brain regions did not.[99]

Other SPECT studies have supported the findings above. In patients with mild cognitive impairment who later develop AD, the presence of temporoparietal (including hippocampal) hypoperfusion,[100] hippocampal–parahippocampal hypoperfusion,[101] and posterior cingulate hypoperfusion,[102] distinguished this population group from patients with normal cerebral perfusion who did not convert to AD during the observation period. Markers that indirectly reflect reduced cerebral perfusion are used with equal success. PET studies for example, have shown that cerebral glucose uptake and

### Search strategy and selection criteria

References for this review were identified by searches of MEDLINE with the terms "Alzheimer's disease", "amyloid", "amyloid hypothesis", "cerebral hypoperfusion", "beta-amyloid", "APP", "risk factors", "pharmacotherapy", "neuroimaging", "mild cognitive impairment", "cardiac disease", "stroke", "atherosclerosis", "senile plaques", "neurofibrillary tangles", "transgenic mice", "memory", "cognition", "dementia", "vascular dementia", "amyloid deposits", "brain", "hippocampus", "cortex", "PS1", "neuronal", "metabolism", and "cerebral blood flow", as well as searches of the names of authors and searches of the references in the selected articles. Papers published until July, 2003, were included. Articles published in English, French, Spanish, Japanese, Italian, German, Hungarian, Swedish, Russian, Chinese, (translations of these papers) were included.

utilisation in the hippocampus of patients with mild cognitive impairment,[103] and in the brains of healthy people who later develop impairment are significantly reduced,[104] suggesting that regional cerebral hypoperfusion is one of the earliest, if not the earliest, marker of AD symptoms. Because cerebral hypometabolism involving low glucose uptake is generally caused by a lowering of cerebral perfusion, AD may be intercepted years before it is expressed and detection probably relies on an abnormal regional pattern of cerebral perfusion.

## Conclusions

A dialectical approach summarising the evidence presented here and that reported elsewhere[37–40] would conclude that there is a causal relation between vascular mechanisms and the development of non-genetic AD, whereas the amyloid hypothesis is an argument that defeats itself when investigated thoroughly. For example, the vascular hypothesis explains how most of the metabolic, biochemical, and physiopathological events develop in AD from an energy crisis secondary to cerebral hypoperfusion;[13–14,75–77] the amyloid hypothesis does not. Many vascular risk factor effects on AD pathology can be shown in laboratory and clinical settings;[42–44,53,84–88] the amyloid effects on AD cannot. The mildly favourable treatment response in patients with AD to therapy that improves cerebral blood flow is a consistent finding;[77,79] the same cannot be said of antiamyloid treatment. The preclinical detection of AD with neuroimaging techniques relies on regional changes in cerebral perfusion;[99–104] no amyloid tests detect AD preclinically.

The data favouring a vascular cause for AD far outweigh that for the amyloid hypothesis. If this is the case, or even if this is only a reasonable possibility, more basic and clinical research on the vascular and metabolic features of AD, more financial support for these investigations, and more tolerance to these ideas are urgently needed.

In my judgment, it is neither untactful nor unreasonable to ask why research up to now has not produced any progress with regards to the clinical management and treatment of AD. The most cogent explanation is that clinical research has been wallowing in its dogmatic think-tank too long and this attitude has suppressed potentially useful thinking that might threaten to subvert its basic canon.

There is much that can be done. There is a need to open more forums for debating the pros and cons of all possible solutions to AD.[105] In the meantime, patients and their physicians should be instructed that AD incidence may be reduced by skilful but aggressive therapy of heart disease, stroke, atherosclerosis and high blood pressure, as well as an assortment of other risk factors accessible to intervention.

#### Acknowledgments

This research was supported by an Investigator-Initiated Research Grant from the Alzheimer's Association.

#### Conflict of interest

I have no conflicts of interest.

#### Role of the funding source

No funding source played a part in the preparation of this review or the decision to submit it for publication.

#### References

1 Masters CL, Simms G, Weinman NA, Multhaup G, McDonald BL, Beyreuther K. Amyloid plaque core protein in Alzheimer disease and Down syndrome. *Proc Natl Acad Sci USA* 1985; **82:** 4245–49.
2 Johnson KA, Lopera F, Jones K, et al. Presenilin-1-associated abnormalities in regional cerebral perfusion. *Neurology* 2001; **56:** 1545–51.
3 Roth M: The natural history of mental disorder in old age. *J Mental Sci* 1955; **101:** 281–301.
4 McKhann G, Drachman D, Folstein R, Katzman R, Price D, Stadlan E. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Services Task Force on AD. *Neurology* 1984; **34:** 939–44.
5 American Psychiatric Association. Diagnostic and statistical manual of mental disorders, fourth edn. Washington DC: American Psychiatric Association, 1994: 138–42.
6 Selkoe DJ. The molecular pathology of Alzheimer's disease. *Neuron* 1991; **6:** 487–98.
7 Glenner GG, Wong CW. Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. *Biochem Biophys Res Commun.* 1984; **120:** 885–90.
8 Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science* 2002; **297:** 353–56.
9 Joseph JA, Shukitt-Hale B, Denisova NA, Martin A, Perry G, Smith MA. Copernicus revisited: amyloid beta in Alzheimer's disease. *Neurobiol Aging* 2001; **22:** 161–63.
10 Davis JN, Chisolm JC. The 'amyloid' cascade hypothesis of AD: decoy or real McCoy? *Trends Neurosci* 1997; **20:** 558–59.
11 Neve R, Robakis NK. Alzheimer's disease: a re-examination of the amyloid hypothesis. *Trends Neurosci* 1998; **21:** 15-19.
12 Bishop GM, Robinson SR. The amyloid hypothesis: let sleeping dogmas lie? *Neurobiol Aging* 2002; **23:** 1101–05.
13 de la Torre JC. Alzheimer's disease: how does it start? *J Alz Dis* 2002; **4:** 497–512.
14 de la Torre JC. Alzheimer's disease as a vascular disorder: nosological evidence. *Stroke* 2002; **33:** 1152–62.
15 Terry RD, Masliah E, Salmon DP, et al. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. *Ann Neurol* 1991; **4:** 572–80.
16 Arriagada PV, Growdon JH, Hedley-White ET, Hyman B. Neurofibrillar tangles but not senile plaques parallel duration and severity of Alzheimer's disease. *Neurology* 1992; **42:** 631–39.
17 Braak H, Braak E. Age, neurofibrillary changes, A-beta and onset of Alzheimer's disease. *Neurosci Lett* 1996; **210:** 87–90.
18 Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiol Aging* 1997; **4:** 351–57.
19 Davis DG, Schmitt FA, Wekstein DR, Markesbery WR. Alzheimer neuropathologic alterations in aged cognitively normal subjects. *J Neuropathol Exp Neurol* 1999; **58:** 376–88.
20 Hatanpää K, Brady DR, Stoll J, Rapoport SI, Chandrasekaran K. Neuronal activity and early neurofibrillary tangles in Alzheimer's disease. *Ann Neurol* 1996; **40:** 411–20.
21 DeCarli C. Post-mortem regional neurofibrillary tangle densities, but not senile plaque densities are related to regional cerebral metabolic rates for glucose during life in Alzheimer disease patients. *Neurodegeneration* 1992; **1:** 11–20.
22 Ji Y, Urakami K, Adachi Y, Maeda M, Isoe K, Nakashima K. Apolipoprotein E polymorphism in patients with Alzheimer's disease, vascular dementia and ischemic cerebrovascular disease. *Dement Geriatr Cogn Disord* 1998; **5:** 243–45.
23 Kalaria RN. The role of cerebral ischemia in Alzheimer's disease. *Neurobiol Aging* 2000; **21:** 321–30.
24 Hsiao K, Chapman P, Nilsen S, et al: Correlative memory deficits, A-beta elevation, and amyloid plaques in transgenic mice. *Science* 1996; **274:** 99–102.
25 Irizarry MC, McNamara M, Fedorchak K, Hsiao K, Hyman BT. PPSw transgenic mice develop age-related A beta deposits and neuropil abnormalities, but no neuronal loss in CA1. *J Neuropathol Exp Neurol* 1997; **56:** 965–73.
26 Koistinaho M, Ort M, Cimadevilla JM, et al. Specific spatial learning deficits become severe with age in beta -amyloid precursor protein transgenic mice that

harbor diffuse beta -amyloid deposits but do not form plaques. *Proc Natl Acad Sci USA* 2001; **98:** 14675–80.
27 Hsiao KK, Borchelt DR, Olson K, et al. Age-related CNS disorder and early death in transgenic FVB-N mice overexpressing Alzheimer amyloid precursor proteins. *Neuron* 1995; **15:** 1203–18.
28 Austin L, Arendash GW, Gordon MN, et al. Short-term beta-amyloid vaccinations do not improve cognitive performance in cognitively impaired APP + PS1 mice. *Behav Neurosci* 2003; **117:** 478–84.
29 Selkoe DJ. Toward a comprehensive theory for alzheimer's disease: hypothesis, Alzheimer's disease is caused by the cerebral accumulation and cytotoxicity of amyloid β protein. *Ann NY Acad Sci* 2000; **924:** 17–25.
30 Robinson SR, Bishop GM. The search for an amyloid solution. *Science* 2002; **298:** 962–64.
31 Steinberg D. Companies halt first Alzheimer vaccine trial. *Scientist* 2002; **16:** 22.
32 Smith MA, Atwood CS, Joseph JA, Perry G. Predicting the failure of amyloid-beta vaccine. *Lancet* 2002; **359:** 1864–65.
33 Perry G, Nunomura A, Raina AK, Smith MA. Amyloid-beta junkies. *Lancet* 2000; **355:** 757
34 Leigh D, Plant JP, Boyle IF, Smith CP, Pearson HA. The production of amyloid-beta peptide Is a critical requirement for the viability of central neurons. *J Neurosci* 2003; **23:** 5531–35.
35 Robinson SR, Bishop GM. Abeta as a bioflocculant: implications for the amyloid hypothesis of Alzheimer's disease. *Neurobiol Aging* 2002; **23:** 1051–72.
36 de la Torre JC, Mussivand T. Can disturbed brain microcirculation cause Alzheimer's disease? *Neurol Res* 1993; **15:** 146–53.
37 de la Torre JC, Hachinski VC, eds. Cerebrovascular pathology in Alzheimer's disease: proceedings of a conference, East Rutherford, New Jersey, Nov 12–15, 1996. *Ann NY Acad Sci* 1997; **826:** 1–519.
38 Kalaria RN, Ince P, eds. Vascular factors in Alzheimer's disease. *Ann NY Acad Sci* 2000; **903:** 1–552.
39 de la Torre JC, ed. Vascular pathophysiology in Alzheimer's disease. *Neurobiol Aging* 2000; **21:** 153–383
40 de la Torre JC, Kalaria RN, Nakajima K, Nagata K, eds. Alzheimer's disease: vascular etiology and pathology. *Ann NY Acad Sci* 2002; **977:** 1–526.
41 Meyer JS, Rauch G, Rauch RA, Haque A. Risk factors for cerebral hypoperfusion, mild cognitive impairment and dementia. *Neurobiol Aging* 2000; **21:** 161–69.
42 Skoog I. The interaction between vascular disorders and Alzhemer's disease. In: The epidemiology of Alzheimer's disease and related disorders: etiology, pathogenesis and therapeutics. Wiley: New York, 1999; 523–30.
43 Skoog I, Gustafson D. Hypertension and related factors in the etiology of Alzheimer's disease. *Ann NY Acad Sci* 2000; **977:** 29–36.
44 Breteler MM. Vascular involvement in cognitive decline and dementia: epidemiologic evidence from the Rotterdam Study and the Rotterdam Scan Study. *Ann NY Acad Sci.* 2000; **903:** 457–65.
45 Pohjasvaara T, Erkinjuntti T, Ylikoski R, Hietanen M, Vataja R, Kaste M. Clinical determinants of poststroke dementia. *Stroke* 1998; **29:** 75–81.
46 Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer's disease: the Nun study. *JAMA* 1997; **277:** 813–17.
47 Kalaria RN. Small vessel disease and Alzheimer's dementia: pathological considerations. *Cerebrovasc Dis* 2002; **13** (suppl 2)**:** 48–52.
48 White L, Petrovitch H, Hardman J, et al. Cerebrovascular pathology and dementia in autopsied Honolulu-Asia Aging Study participants. *Ann NY Acad Sci* 2002; **977:** 9–23
49 Tatemichi TK, Paik M, Bagliella E, et al. Risk of dementia after stroke in a hospitalized cohort: results of a longitudinal study. *Neurology* 1994; **44:** 1885–91.
50 Schmidt R. Comparison of magnetic resonance imaging in Alzheimer's disease, vascular dementia and normal aging. *Eur Neurol* 1992; **32:** 164–69.
51 Pasquier F, Henon H, Leys D. Relevance of white matter changes to pre- and poststroke dementia. *Ann NY Acad Sci* 2000; **903:** 466–69.
52 Suter OC, Sunthorn T, Kraftsik R, et al. Cerebral hypoperfusion generates cortical watershed microinfarcts in Alzheimer disease. *Stroke* 2002; **33:** 1986–92.
53 Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med* 2003; **348:** 1215–22.
54 Kwan LT, Reed BR, Eberling JL, et al. Effects of subcortical cerebral infarction on cortical glucose metabolism and cognitive function. Arch Neurol 1999; **56:** 809–14.
55 Vermeer SE, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM.Prevalence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. *Stroke* 2002; **33:** 21–25
56 O'Connell JE, Gray CS, French JM, Robertson IH. Atrial fibrillation and cognitive function: case-control study. *J Neurol Neurosurg Psychiatry* 1998; **65:** 386–89.
57 Vermeer SE, Den Heijer T, Koudstaal PJ, et al. Incidence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. *Stroke* 2003; **34:** 392–96.
58 Alter M, Zhang ZX, Sobel E, Fisher M, Davanipour Z, Friday G. Standardized incidence ratios of stroke: a worldwide review. *Neuroepidemiology.* 1986; **5:** 148–58.
59 Aronson MK, Ooi WL, Morgenstern H, et al. Women, myocardial infarction, and dementia in the very old. *Neurology* 1990; **40:** 1102–06
60 Ott A, Breteler MM, de Bruyne MC, van Harskamp F, Grobbee DE, Hofman A. Atrial fibrillation and dementia in a population-based study: the Rotterdam Study. *Stroke* 1997; **28:** 316–21.
61 Polidori MC, Marvardi M, Cherubini A, Senin U, Mecocci P. Heart disease and vascular risk factors in the cognitively impaired elderly: implications for Alzheimer's dementia. *Aging (Milan)* 2001; **13:** 231–39.
62 Sparks DL. Coronary artery disease, hypertension, ApoE, and cholesterol: a link to Alzheimer's disease? *Ann NY Acad Sci* 1997; **826:** 128–46.
63 Newman MF, Kirchner JL, Phillips-Bute B, et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. *N Eng J Med* 2001; **344:** 395–402.
64 Brillman J. Central nervous system complications in coronary artery bypass graft surgery. *Neurol Clin* 1993; **11:** 475–95.
65 Selnes OA, Goldsborough MA, Borowicz L, Enger C, Quaskey S, McKhann GM. Determinants of cognitive change after coronary artery bypass surgery: a multifactorial problem. *Ann Thorac Surg* 1999; **67:** 1669–76.
66 Hofman A, Breteler MM, Bots ML, Slooter AJ, van Harskamp F. Atherosclerosis, apolipoprotein E and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. *Lancet* 1997; **349:** 151–54.
67 Qiu C, Winblad B, Viitanen M, Fratiglioni L. Pulse pressure and risk of Alzheimer disease in persons aged 75 years and older: a community-based, longitudinal study. *Stroke* 2003; **34:** 594–99.
68 Aliev G, Seyidova D, Neal ML, et al. Atherosclerotic lesions and mitochondria DNA deletions in brain microvessels as a central target for the development of human AD and AD-like pathology in aged transgenic mice. *Ann NY Acad Sci* 2002; **977:** 45–64.
69 de la Torre JC, Stefano GB. Evidence that Alzheimer's disease is a microvascular disorder: role of constitutive nitric oxide. *Brain Res Rev* 2000; **34:** 119–36.
70 Lunn S, Crawley F, Harrison M, Brown MM, Newman SP. Impact of carotid endarterectomy upon cognitive functioning: a systematic review of the literature. *Cerebrovasc Dis* 1999; **9:** 74–81.
71 de la Torre JC, Pappas BA, Prevot V, et al. Hippocampal nitric oxide upregulation precedes memory loss and $A\beta_{1-40}$ accumulation after chronic brain hypoperfusion in rats. *Neurol Res* 2003; **25:** 635–41.
72 Bakker FC, Klijn CJ, Jennekens-Schinkel A, Kappelle LJ. Cognitive disorders in patients with occlusive disease of the carotid artery: a systematic review of the literature. *J Neurol* 2000; **247:** 669–76 .
73 Sinforiani E, Curci R, Fancellu R, Facchinetti P, Mille T, Bono G. Neuropsychological changes after carotid endarterectomy. *Funct Neurol* 2001; **16:** 329–36.
74 Heyer EJ, Adams D, Solomon RA, et al. Neuropsychometric changes in patients after carotid endarterectomy. *Stroke* 1998; **29:** 1110–15.
75 de la Torre JC. Critical threshold cerebral hypoperfusion causes Alzheimer's disease. *Acta Neuropathol* 1999; **98:** 1–8.
76 de la Torre JC. Critically-attained threshold of cerebral hypoperfusion: the CATCH hypothesis of Alzheimer's pathogenesis. *Neurobiol Aging* 2000; **21:** 331–42.
77 de la Torre JC. Hemodynamic consequences of deformed microvessels in the brain in Alzheimer's disease. *Ann NY Acad Sci* 1997; **826:** 75–91.
78 Frankish H. NSAIDs do not slow Alzheimer's progression. *Lancet* 2003; **361:** 1964.
79 Knopman D. Pharmacotherapy for Alzheimer's disease: 2002. *Clin Neuropharmacol* 2003; **26:** 93–101.
80 Gold PE, Cahill L, Wenk GL. The lowdown on Ginkgo biloba. *Sci Am* 2003; **288:** 86–91.
81 de la Torre JC. Hemodynamic consequences of deformed microvessels in the brain in Alzheimer's disease. *Ann NY Acad Sci* 1997; **826:** 75–91.
82 Roland PE, Friberg L. Localization of cortical areas activated by thinking. *J Neuropathol* 1985; **53:** 1219–43.
83 Ball LJ, Birge SJ. Prevention of brain aging and dementia. *Clin Geriatr Med* 2002; **18:** 485–503.
84 de la Torre JC, Fortin T, Park G, Pappas B, Saunders J, Richard M. Brain blood-flow restoration "rescues" chronically damaged rat CA1 neurons. *Brain Res* 1993; **623:** 6–15.
85 De Jong GI, Farkas E, Stienstra CM, et al**.** Cerebral hypoperfusion yields capillary damage in hippocampus CA1 that correlates to spatial memory impairment. *Neuroscience* 1999; **91:** 203–10.
86 Farkas E, De Jong GI, de Vos RA, Jansen Steur EN, Luiten PG. Pathological features of cerebral cortical capillaries are doubled in Alzheimer's disease and Parkinson's disease. *Acta Neuropathol (Berl)* 2000; **100:** 395–402.
87 De Jong GI, De Vos RAI, Janssen-Steur E, Luiten PG: Cerebrovascular hypoperfusion: a risk factor for Alzheimer's disease? Animal model and postmortem human studies. *Ann NY Acad Sci* 1997; **826:** 56–74.
88 Aliev G, Seyidova D, Lamb BT, et al. Mitochondria and vascular lesions as a central target for the development of Alzheimer's disease and Alzheimer disease-like pathology in transgenic mice. *Neurol Res* 2003; **25:** 665–74.
89 Mancardi GL, Perdelli F, Leonardi A, Bugiani O. 1980. Thickening of the basement membrane of cortical capillaries in Alzheimer's disease. *Acta Neuropathol* **49:** 79–83.
90 Buée L, Hof PR, Delacourte A. Brain microvascular changes in Alzheimer's disease and other dementias. *Ann NY Acad Sci* 1997; **826:** 7–24.
91 Kawamoto A, Asahara T, Losordo DW. Transplantation of endothelial progenitor cells for therapeutic neovascularization. *Cardiovasc Radiat Med* 2002; **3:** 221–25.
92 Asahara T, Murohara T, Sullivan A, et al. Isolation of putative progenitor endothelial cells for angiogenesis. *Science* 1997; **275:** 964–67.
93 Takahashi T, Kalka C, Masuda H, et al. Ischemia- and cytokine-induced mobilization of bone marrow-derived endothelial progenitor cells for neovascularization. *Nat Med* 1999; **5:** 434–38.
94 Kocher AA, Schuster MD, Szabolcs MJ, et al. Neovascularization of ischemic myocardium by human bone-marrow-derived angioblasts prevents cardiomyocyte apoptosis, reduces remodeling and improves cardiac function. *Nat Med* 2001; **7:** 430–36.
95 Luttun A, Carmeliet G, Carmeliet P. Vascular progenitors: from biology to treatment. *Trends Cardiovasc Med* 2002; **12:** 88–96
96 Hill JM, Zalos G, Halcox JP, et al. Circulating endothelial progenitor cells, vascular function, and cardiovascular risk. *N Engl J Med* 2003; **348:** 593–600.
97 Asahara T, Masuda H, Takahashi T, et al. Bone marrow origin of endothelial progenitor cells responsible for postnatal vasculogenesis in physiological and pathological neovascularization. *Circ Res* 1999; **85:** 221–28.
98 Shah S, Tangalos EG, Petersen R. Mild cognitive impairment: when is it a precursor of Alzheimer's disease? *Geriatrics* 2000; **55:** 65–68.
99 Johnson KA, Albert MS. Perfusion abnormalities in prodromal Alzheimer's disease. *Neurobiol Aging* 2000; **21:** 289–92.
100 Kogure D, Matsuda H, Ohnishi T, et al. Longitudinal evaluation of early Alzheimer's disease using brain perfusion SPECT. *J Nucl Med* 2000; **41:** 1155–62.
101 Okamura N, Shinkawa M, Arai H, Matsui T, Kakajo K, Maruyama M. Prediction of progression in patients with mild cognitive impairment using IMP-SPECT. *Nippon Ronen Igakkai Zasshi* 2000; **37:** 974–78.
102 Rodriguez G, Vitali P, Calvini P, et al. Hippocampal perfusion in mild cognitive impairment. *Psychiatry Res* 2000; **100:** 65–74.
103 De Santi S, de Leon MJ, Rusinek H, Convit A, Tarshish C, Roche A. Hippocampal formation glucose metabolism and volume losses in MCI and AD. *Neurobiol Aging* 2001; **22:** 529–39.
104 de Leon M, Convit A, Wolf OT, et al. Prediction of cognitive decline in normal elderly subjects with 2-[(18)F] fluoro-2-deoxy-D-glucose/positron-emission tomography (FDG/PET). *Proc Natl Acad Sci USA* 2001; **98:** 10966–71.
105 Kachaturian Z, Mesulam MM (eds). Alzheimer's disease: a compendium of current theories. *Ann NY Acad Sci* 2000; **924:** 1–193.