Vascular Basis of Alzheimer's Pathogenesis

J. C. DE LA TORRE

Division of Neuropathology, University of California, San Diego, San Diego, California, USA

ABSTRACT: Considerable evidence now indicates that Alzheimer's disease (AD) is primarily a vascular disorder. This conclusion is supported by the following evidence: (1) epidemiologic studies linking vascular risk factors to cerebrovascular pathology that can set in motion metabolic, neurodegenerative, and cognitive changes in Alzheimer brains; (2) evidence that AD and vascular dementia (VaD) share many similar risk factors; (3) evidence that pharmacotherapy that improves cerebrovascular insufficiency also improves AD symptoms; (4) evidence that preclinical detection of potential AD is possible from direct or indirect regional cerebral perfusion measurements; (5) evidence of overlapping clinical symptoms in AD and VaD; (6) evidence of parallel cerebrovascular and neurodegenerative pathology in AD and VaD; (7) evidence that cerebral hypoperfusion can trigger hypometabolic, cognitive, and degenerative changes; and (8) evidence that AD clinical symptoms arise from cerebromicrovascular pathology. The collective data presented in this review strongly indicate that the present classification of AD is incorrect and should be changed to that of a *vascular disorder.* Such a change in classification would accelerate the development of better treatment targets, patient management, diagnosis, and prevention of this disorder by focusing on the root of the problem. In addition, a theoretical capsule summary is presented detailing how AD may develop from chronic cerebral hypoperfusion and the role of *critically attained threshold of cerebral hypoperfusion* (CATCH) and of vascular nitric oxide derived from endothelial nitric oxide synthase in triggering the cataclysmic cerebromicrovascular pathology.

KEYWORDS: Alzheimer's disease (AD); vascular dementia (VaD); cerebral hypoperfusion; brain; vascular disorder

INTRODUCTION

There is now substantial evidence from the fields of epidemiology, pharmacology, neuroimaging, clinical medicine, histopathology, and molecular biology strongly supporting the position that sporadic Alzheimer's disease (AD) is a disorder of the vascular system in the aging subject.

We have reviewed much of this evidence elsewhere[1–6] and will briefly outline here the major findings that support the conclusion that AD is a vascular disorder with neurodegenerative consequences rather than a neurodegenerate disorder with vascular consequences. The latter has been the accepted paradigm for the last 20

Address for correspondence: J. C. de la Torre, M.D., Ph.D., UCSD-Neuropathology, 1363 Shinly, Suite 100, Escondido, CA 92026. Voice: 760-743-7441; fax: 760-747-3313.
jdelator@nctimes.net

Ann. N.Y. Acad. Sci. 977: 196–215 (2002).

years. The question of whether AD has its causal roots in vasculopathic or neurodegenerative processes is of critical importance if doors to new research avenues are to open and patients with this dementia are to benefit more than in the past with respect to improved management and treatment.

If indeed AD is a vascular disorder that initiates its pathology through cerebral microvascular abnormalities,[1,2,6] then its origin, clinical signs, diagnosis, and potential treatment should revolve around a "vasculopathic complex" that provides its defining qualities. This appears to be the case because AD has been identified with the following evidence:

- epidemiologic evidence linking vascular factors to cerebrovascular pathology that can set in motion metabolic, neurodegenerative, and cognitive changes in Alzheimer brains;
- evidence that AD and vascular dementia (VaD, defined here as a "post-stroke-hypoperfusion" dementia) share similar risk factors;
- evidence that pharmacotherapy that improves cerebrovascular insufficiency also improves AD symptoms;
- evidence that pharmacotherapy that benefits AD also benefits VaD;
- evidence that preclinical or prodromal detection of potential AD is possible from direct or indirect regional cerebral perfusion measurements;
- evidence of overlapping clinical symptoms in AD and VaD;
- evidence that shows parallel cerebrovascular and neurodegenerative pathology in AD and VaD;
- evidence that cerebral hypoperfusion can trigger hypometabolic, cognitive, and degenerative changes;
- evidence that AD clinical symptoms arise from cerebromicrovascular pathology, particularly involving endothelial cells and vascular nitric oxide dysfunction.

EPIDEMIOLOGIC EVIDENCE

The Rotterdam Study is one of the most important epidemiologic studies to examine risk factors associated with AD. The Rotterdam Study includes over 7000 elderly people who have been identified since 1990 and consists of demented subjects and nondemented, age-matched controls.[7] The dementia group was further divided into vascular and Alzheimer's dementia using accepted neurological, neuroimaging, and psychological screening techniques.[7,8]

Based on the collective data gathered by the Rotterdam Study, it was concluded that vascular risk factors, and indicators of vascular disease, particularly in elderly subjects, have an established association with AD.[9,10] The risk factors for AD reported thus far in the Rotterdam Study, many of which have been confirmed by other independent studies, include hypertension,[10] diabetes mellitus,[11,12] thrombotic episodes,[13] high serum homocysteine,[14] atrial fibrillation,[15] smoking,[16,17] alcoholism,[18] low level of education,[19] high serum cholesterol,[8,10] and atherosclerosis[20] (TABLE 1).

TABLE 1. Reported Alzheimer risk factors

- aging
- atherosclerosis ∇
- stroke ∇
- lower education
- diabetes mellitus ∇
- smoking ∇
- alcoholism
- hi HDL-cholesterol ∇
- cardiac disease ∇
- migraine ∇
- cardiac arrhythmias
- hi serum viscosity
- thrombogenic factors ∇
- apoE4 genotype
- hi serum homocysteine ∇
- hypertension ∇
- hypotension
- hi fibrinogen levels
- head injury-LOC
- menopause ∇
- transient ischemic attack
- hi fat intake
- microvessel pathology ∇

NOTE: Reported risk factors for AD compiled from epidemiologic studies of elderly subjects. Despite the discrete etiogenesis, pathologic course, and clinical outlook of each risk factor, they are linked by two characteristics: (1) all are vascular-related and (2) all impair or reduce cerebral perfusion. In addition, about one-half of the risk factors listed are associated with vascular NO dysfunction (∇). It should be noted that most of the risk factors listed here are also risk factors for VaD. See text for details.

KEY: HDL, high-density lipoprotein:cholesterol ratio; apoE4, apolipoprotein E–ε4 allele; LOC, loss of consciousness.

Other epidemiologic studies have reported additional vascular-related risk factors for AD in addition to confirming many of those mentioned above: migraine,[21] high intake of saturated fat,[22] presence of APOE4 allele,[23,24] transient ischemic attacks,[25] high serum cholesterol levels,[24] depression,[26,27] alcoholism,[25,28] high serum homocysteine levels,[29,30] menopause,[31,32] high fibrinogen concentrations,[33] hemorheologic abnormalities,[34,35] hypotension,[35–38] ischemic stroke,[39,40] head injury,[41–43] cardiac disease including arrhythmias,[44,45] and aging[46] (the most important risk factor of all). Most of these risk factors are present not only in the early stages of AD, but often decades before any cognitive symptoms develop[19,20,25,29,30,33,36,38,40,43] (TABLE 1). All these conditions have a vascular involvement and are known to reduce cerebral perfusion.[4–6]

Thus, despite the discrete pathologies involved in each of these risk factors, as well as their different clinical course and outlook, all share one common action: the reduction or impairment of optimal cerebral perfusion[1–6] (TABLE 1). By applying elementary statistics, the possibility that these reported AD risk factors share a single,

common biological pathology that is due to chance alone is highly improbable. In addition, we can think of no other common denominator that connects these risk factors more fittingly than the link to vascular pathology. It is worthwhile to note that many of the risk factors described for AD are also associated with vascular nitric oxide dysfunction.[47] This activity by vascular nitric oxide will be discussed below.

Not surprisingly, most of the AD risk factors mentioned above are also risk factors for VaD (TABLE 1). This relationship, if considered only by itself, suggests that these two dementias share a common origin. It should be noted that about 30% of all AD brains show some form of cerebrovascular pathology, and practically *all* AD brains reveal periventricular white matter lesions, microvessel degeneration, cerebral amyloid angiopathy, or combinations of these lesions;[48] the connection between AD and VaD appears more than coincidental. The flip side of the coin is equally intriguing because about 40% of brains meeting clinical VaD diagnosis have concurrent AD pathologic deposits involving senile plaques and fibrillary tangles.[49] Moreover, difficulties in diagnosing AD from VaD on clinical grounds alone are well known,[50] creating the suspicion that their pathophysiologic roots are offshoots of a common source.

Taking a moment to reflect on these correlations that appear to fuse these two dementias, a reasonable explanation emerges for the cerebrovascular component seen in some AD brains, which is arguably due to "mixed" dementia, that is, pathologic lesions characteristic of AD and VaD existing comorbidly, and as a separate entity from a "pure" dementia where only neurodegenerative lesions (AD) or cerebrovascular lesions (VaD) are present. However, this argument does not explain why "pure" AD still retains a powerful vascular basis. For example, as shown in TABLE 1, many of the risk factors reported for AD, such as atherosclerosis, cardiac disease, diabetes, etc., are not in themselves cerebrovascular events characteristic of VaD. In fact, these reported risk factors appear to convert just as easily to VaD as they do to AD.[20,51–53] It should be recalled that VaD usually arises from immediate ischemic, hemorrhagic, hypoxic, or anoxic events and, as seen from TABLE 1, AD can develop from other conditions that might not give exclusive rise to VaD.

PHARMACOLOGIC TREATMENTS FOR AD

There is no drug treatment at the present time that is truly effective in the treatment of AD or in altering the course of this disorder. Only three drugs have been approved in the United States for prescriptive use in AD: Cognex (tacrine), Aricept (donepezil), and Exelon (rivastigmine tartrate). All three act to block the synaptic breakdown of acetylcholine, a neurotransmitter important in memory and learning. A fourth drug, Reminyl (galantamine hydrobromide), targets "mixed" dementia, that is, VaD or AD complicated by cerebrovascular pathology. Mixed dementia is presently more common than AD or VaD.[54]

These treatments generally provide modest damage control at the early stages of AD and offer minor to no improvement at later stages of the disease. For this reason, other drug therapies for AD have been tried, including nonsteroidal anti-inflammatory agents (NSAIDs),[55] ginkgo biloba,[56,57] estrogen during menopause,[58–60] dimethyl sulfoxide,[61] aspirin,[62] vitamin E,[63,64] acetyl-L-carnitine,[65,66] antihypertensives,[67] statins,[68,69] and selegiline.[70] While the biologic activity and pharmacokinetics of

these compounds differ from one another, and their effect in reducing the symptoms or delaying the progress of AD is debatable, they all share to a degree one common effect: namely, to improve or increase cerebral perfusion.

PRODROMAL DETECTION OF AD

There is now good evidence that a transitional stage of AD begins with mild cognitive impairment (MCI), defined as memory dysfunction with preservation of other cognitive and functional activities.[71–73] Identifying MCI means that AD diagnosis and preventive treatment can be applied much earlier than previously practiced. One technique that offers such preclinical assessment of AD during the MCI stage is based on detection of cerebral hypoperfusion patterns using SPECT or PET among individuals complaining only of memory problems. In one study, subjects with memory complaints not meeting ADRDA criteria for AD had their regional CBF measured using SPECT and they were separated into two groups. The majority of the subjects with significant hypoperfusion of the hippocampal-amygdaloid complex (areas linked to memory function) converted to AD within a 3-year follow-up, while patients with normal cerebral perfusion in these and other brain areas did not.[74,75]

Other neuroimaging studies have supported the above findings. In MCI patients who later converted to AD, the presence of temporoparietal (including hippocampal) hypoperfusion,[76] hippocampal-parahippocampal hypoperfusion,[77] and posterior cingulate hypoperfusion[78] distinguished this population group from non-MCI subjects. Other markers indirectly reflecting reduced cerebral perfusion are used with equal success. Positron emission tomography (PET), when used to measure cerebral glucose metabolism, shows specific decline of glucose metabolic rate utilization in the hippocampus in subjects with MCI[79,80] and in the brains of subjects who later convert to MCI.[81] Cerebral hypometabolism is generally caused by a lowering of cerebral perfusion.

AD-VaD CORRELATES

The differential diagnosis of Alzheimer and vascular dementia based on clinical grounds is at best very difficult.[82–84] This problem exists because of overlapping features found in both disorders. For example, AD and VaD share features involving cerebral hypoperfusion, white matter changes,[85–87] pathophysiologic markers,[88–92] genetic links,[93–96] overlapping symptoms, and diagnostic criteria of dubious reliability.[97–104] Several objective clinical criteria are presently used to distinguish AD from VaD, such as from the Alzheimer Disease Diagnostic and Treatment Centers (ADDTC), the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN), the Diagnostic and Statistical Manual of Mental Disorders (fourth edition) (DSM-IV), and the Hachinski Ischemia Score.[105] The use of CT or MRI neuroimaging contributes little to characterizing either dementia when white matter changes and medial temporal atrophy are involved.[106]

Recently, it was reported that both AD and VaD patients release intrathecal vascular endothelial growth factor (VEGF) and transforming growth factor-beta

(TGF-β) locally,[107] two cytokines that modulate angiogenesis following ischemia-hypoxia. The intrathecal levels of these two molecules appear related to disease severity of AD and VaD and are associated with intrathecal levels of Aβ.[107] The findings suggest that vascular factors play a pathogenic role not only in VaD, but also in AD. The collective data argue in favor that AD and VaD are not mutually exclusive disorders.

CEREBRAL HYPOPERFUSION AND HYPOMETABOLISM IN AD

The collective findings discussed thus far suggest that brain hypoperfusion precedes the hypometabolic and neurodegenerative state seen in AD. This is a logical assumption based on Darwinian rules of survival since it would seem unlikely that neurons exposed to oxidative stress and impaired energy substrate delivery would further reduce blood flow to accelerate their death. Moreover, the conclusion that brain hypoperfusion "pushes" oxidative stress, cognitive decline, and neurodegeneration is further reinforced by the following six findings.

First, regional microvessel degeneration is independent of AD stage severity (Braak I–VI), a finding that indicates these microvascular changes are not a consequence of AD pathology.[108] Second, regional hypometabolism found in Alzheimer brains does not appear to result from neurodegenerative damage or senile plaque formation, but is present prior to significant tissue pathology.[109,110] Third, abundant density of senile plaques, neurofibrillary tangles (NFTs), and neurodegenerative changes that met neuropathologic criteria for AD have been found in a large percentage of cognitively normal, elderly brains at autopsy.[111] Fourth, the same structural capillary aberrations seen in AD have been observed also in Down's syndrome at a young age, when no senile plaque or NFT has yet formed.[112] Fifth, young patients with Down's syndrome show abnormal patterns of cerebral perfusion similar to those found in AD at an age when senile plaques and NFTs are still absent from their brains and before any dementia symptoms are manifested.[113,114] Sixth, oxidative stress seems to precede $A\beta_{1-42}$ deposition by many years in Down's syndrome subjects who die in their teens and twenties,[115] a finding that indicates amyloid-β pathology is not the trigger of neuronal metabolic disruption in Down patients and, by deduction, nor is it in AD.

The argument that hypometabolism in AD may elicit microvascular changes at some point is not supported by a considerable number of animal experiments that reveal that chronic brain hypoperfusion can trigger oxidative stress, energy metabolic deficits, and memory loss *before* any neuronal structural pathology materializes,[116–126] whereas there are no data that we are aware of that indicate the reverse process can or does occur. Moreover, the recent discovery of "neuroglobin" in rodent and human brain could partly explain why CA1 hippocampal neurons are exquisitely sensitive to hypoperfusion leading to hypometabolism.[127] Neuroglobin in brain appears to act much like myoglobin in cardiac muscle cells; it aids oxygen diffusion to the mitochondria. Lower resistance by CA1 to ischemia may be due to lower oxygen supply resulting from less available neuroglobin, whose lowest expression is in the hippocampus.[127] Consequently, brain hypoperfusion could reduce neuroglobin levels in CA1 and initiate mitochondrial oxidative stress.

THEORETICAL BASIS OF AD PATHOGENESIS

We have previously proposed a theoretical scheme that fits well with the vascular basis of Alzheimer pathogenesis. In this scheme, AD would begin when at least two biological events converge: *advanced aging* and *the presence of a vascular risk factor for AD* (TABLE 1). These two events create a critically attained threshold of cerebral hypoperfusion (CATCH).[4,128,129] CATCH is an unremitting and progressive hemodynamic deficiency affecting cerebral capillaries in specific brain regions that will ultimately destabilize neurons, synapses, neurotransmission, and intellectual function, creating in its wake *regional* neurodegenerative lesions characterized by the formation of senile plaques, NFTs, and amyloid angiopathy.

FIGURE 1 shows a theoretical sketch of how CATCH may develop. From an early age, CBF shows a tendency to normally decline with time. The older we get, the less blood flow reaches the brain.[130] Ordinarily, this is not a problem (white circles, FIG. 1) unless an additional burden to CBF, such as an AD risk factor that can further lower cerebral perfusion (TABLE 1). If a cerebrovascular-lowering condition is expressed, CBF can reach a "critical flow level" (black squares, FIG. 1) beginning in the fifth decade of life or even before. Reaching a "CATCH flow level" has a variable time course and may depend not only on age, but on state of health, lifestyle,

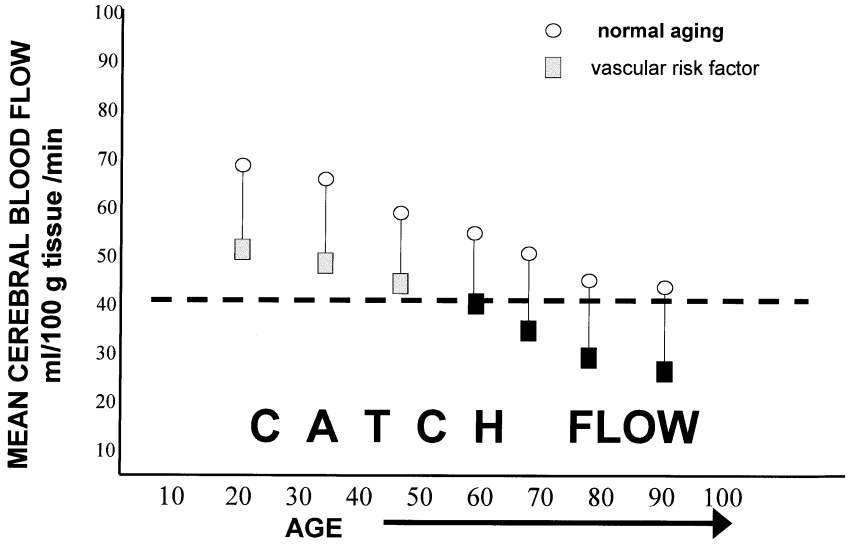

FIGURE 1. Theoretical sketch showing how Alzheimer's disease (AD) may develop. *White circles* correspond to normal decline of cerebral blood flow (CBF) during aging. Note that critically attained threshold of cerebral hypoperfusion (CATCH) flow is not necessarily reached even at the ninth decade of life (*dashed line*). However, if CBF is burdened by a condition (see TABLE 1) that further reduces cerebral perfusion, such as from a vascular risk factor for AD (*gray squares*), CATCH flow (an arbitrary flow value) and suboptimal delivery of energy substrates are reached much sooner during aging (*black squares*). When CATCH flow is reached, neuronal energy compromise may begin a metabolic cycle that eventually involves the cellular and subcellular pathology known to result in AD.

genetics, gender, diet, environmental exposure, and other confounding factors. When CATCH reaches the critical flow level, a chain of events involving subcellular and energy-related metabolic abnormalities are expressed in ischemic-sensitive neuronal populations located mainly in the hippocampus and entorhinal cortex. The outcome of this process is initially gradual and then accelerates to create cognitive dysfunction, beginning with mild visuospatial memory changes (mild cognitive impairment) and terminating in severe cognitive failure. During this neuronal-energy crisis, histopathologic elements of tissue breakdown in the form of senile plaques and NFTs may appear.

Curiously, memory function, as with CBF, also appears to decline with time.[131] When healthy subjects from the ages of 20–80 were examined for cerebral functional changes using MRI, hippocampal signals were observed to decline with advancing age and, in some elderly subjects, showed a pathological decline suggestive of an incipient dementia.[131] Memory decline in relation to aging probably follows a similar curve as CBF during aging and at some point can become disabling when accompanied by vascular pathology (FIG. 1). The driven pathologic process further pushes normal cerebral perfusion to CATCH and eventually AD expression.

The metabolic and biochemical cycle initiated by CATCH results from lowered delivery of glucose and oxygen to neurons and glia (FIG. 2). Brain metabolic energy is almost exclusively served by a steady supply of glucose, which together with oxygen generates the main fuel of the brain, adenosine triphosphate (ATP).[132] Lowered ATP production stemming from chronic brain hypoperfusion triggers a

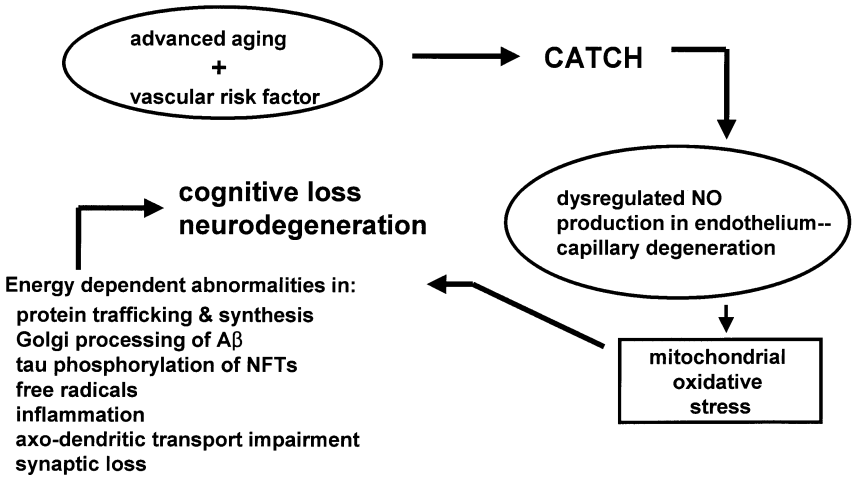

FIGURE 2. Proposed pathogenic evolution of Alzheimer's disease. Theoretical sketch showing how, after CATCH is reached, dysregulation of endothelial NO production leading to capillary degeneration triggers mitochondrial oxidative stress resulting from impaired delivery of energy substrates, glucose and oxygen. The resulting energy crisis further leads to cellular and subcellular pathology involving protein synthesis, development of plaques and tangles, inflammation, and synaptic damage, a collection of neurodegenerative changes associated with progressive cognitive failure.

series of metabolic events characterized by increased hippocampal-glial activation and oxidative stress.[133] Depressed ATP levels further drain energy metabolism and weaken mitochondrial oxidation of glucose, cytochrome oxidase levels, and aerobic glycolysis[132,134] (FIG. 2). This neuronal-energy drain reflecting hemodynamic compromise has been reviewed by us in previous publications.[3,5,47,128,129]

PROTEIN ABERRATION AND FORMATION OF Aβ AND NFTs

The subcellular organelles where protein aberrations can occur are the endoplasmic reticulum (ER) and the Golgi complex. Brain ischemia is reported to disturb the function of the ER more in the hippocampus than in the cortex.[135,136] This is an intriguing piece of information considering that (1) aminoacylation (the adding of an amino acid to a tRNA molecule) requires ATP to drive the enzymatic reaction and (2) the hippocampus is known to be a region extremely vulnerable to ischemia. Consequently, if tRNA is altered in some way by suboptimal availability of energy substrates, mutations of specific proteins (see below) can damage or block the cell's ability to carry out normal cytoplasmic functions. Correct amino acid sequence and protein folding during protein synthesis require high-energy consumption, and disturbances of such protein synthesis can injure the neuron from within.[137] Thus, it seems reasonable that a dysfunctional ER in ischemic-sensitive neuronal populations following CATCH can cause $A\beta_{42}$ to accumulate intracellularly and be secreted extracellularly.[138]

One function of the Golgi complex is to modify and sort secretory particles from the ER and then transport them for release in terminals.[139] This process may be relevant to AD because recent data show that $A\beta_{1-40}$ is generated and packaged into secretory vesicles exclusively in the Golgi, whereas $A\beta_{1-42}$ is made and retained within the ER in an insoluble form and then somehow secreted extracellularly.[140,141] Both $A\beta_{40}$ and $A\beta_{42}$ peptides are known to accumulate excessively in selected Alzheimer brain regions, but $A\beta_{42}$ appears more toxic of the two and is believed to form the core of senile plaques.[142]

The mechanism governing fast-transported proteins requires that they cross the Golgi complex where some proteins are modified posttranslationally by proteolytic cleavage, glycosylation, and phosphorylation, and then packaged into vesicles and transported to axons or dendrites where they are propelled by motor proteins attached to microtubules.[143–146] This orderly cytoskeletal traffic moves axonally in both directions (anterograde and retrograde transport) and requires energy in the form of ATP. When energy substrate supply is inadequate, intracellular transport, including fast axonal transport, becomes dysfunctional and contributes to synaptic and neurotransmission loss followed by cell death.[147] In addition, microtubule "ties" or cross-bridges that keep microtubule "tracks" together by the protein tau would undergo permanent disassembly from inability of energy-deficient motor proteins to transport axonal proteins, including tau, to their source. Disassembly of microtubule cross-bridges would result in the formation of *paired helical filaments*, which ultimately coalesce into NFTs, a marker of AD pathology. Because retrograde axonal transport from the terminal to the cytoplasm requires energy, dysregulation of this shuttling mechanism would also affect growth and trophic factors (generally picked up at the nerve ending by pinocytosis) needed for cell survival and protection from such insults as chronic ischemia.

ROLE OF VASCULAR NITRIC OXIDE IN AD

What is the primary signal for AD neurodegeneration? In our judgment, nitric oxide malfunction, particularly that derived from endothelial nitric oxide synthase (eNOS), may be the pivotal factor in the pathogenesis of AD. This conclusion is supported by a number of basic and clinical studies that we will briefly mention here. Nitric oxide (NO) is the enzymatic product of nitric oxide synthase (NOS), which exists in three isoforms in brain: eNOS, found mostly in the plasma membrane caveolae of endothelial cells (producer of vascular NO); neuronal NOS (nNOS), localized mainly in neurons; and inducible NOS (iNOS), released by neurons and glia after cytokine or endotoxin activation. All three isoforms are aberrantly expressed in AD and are often seen in direct association with Aβ brain deposits.[148]

Release of NO from cerebral endothelial cells to produce vasodilation is a fairly well established reaction.[149,150] NO produced by eNOS plays a key role in vascular tone, blood pressure, and vascular homeostasis and acts to inhibit platelet and leukocyte adhesion to the endothelium, a process that may downregulate proinflammatory

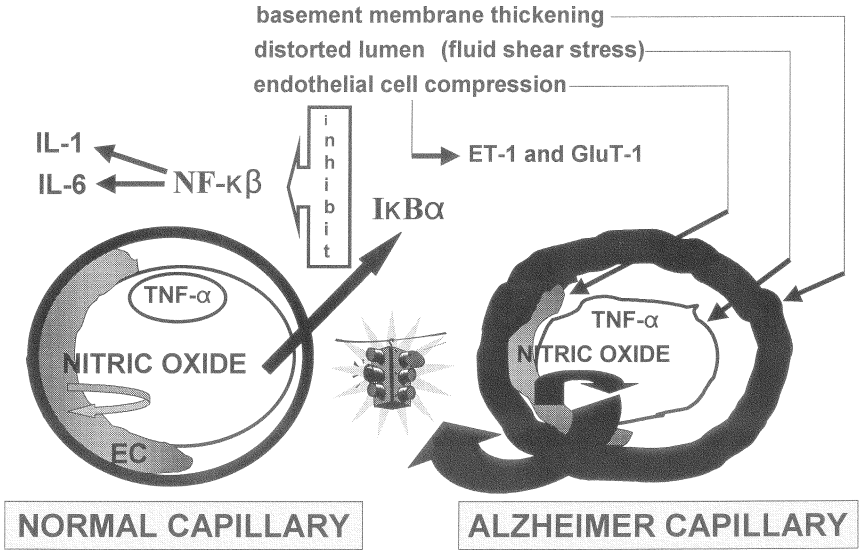

FIGURE 3. Normal hippocampal cerebral capillary shows homeostatic release and uptake of NO from endothelial cells in support of endothelial cell conformation, optimal local blood flow, stabilization of the NF-κβ inhibitor IκBα, and mediation of TNF-α-induced NF-κβ activation. Structural capillary distortion may occur from shear stress changes during chronic cerebral hypoperfusion, eventually reducing basal levels of NO. Low basal levels of NO are unable to mediate TNF-α induction of NF-κβ activation and resulting cytokine production (IL-1, IL-6) and proinflammatory intracellular events. Basement membrane thickening and endothelial cell shape changes may result from low basal levels of NO, a process that would allow abnormal release of the powerful vasoconstrictor, endothelin-1 (ET-1), and impair glucose transporter-1 (GluT-1) from transporting plasma glucose across the blood-brain barrier.

events.[151–153] Vascular NO therefore acts as an antiatherogenic, antithrombotic, and anti-ischemic molecule by reducing oxidative stress, by preventing platelet aggregation, and by stimulating angiogenesis via VEGF, while reducing shear stress on the vessel wall, consequently protecting endothelial cell function.[47,154]

NO has been shown to diffuse toward the lumen of blood vessels in humans where it helps maintain blood fluidity[155] and, by inference, to reduce blood viscosity and resistance, thus improving flow. However, normal blood flow can be hemodynamically compromised via physical or chemical stimuli affecting eNOS levels localized in the endothelial cell caveolae (small invaginations in the plasma membrane of endothelial cells involved in cell signaling) (FIG. 3). When that happens, abnormal movements in pressure or fluid shear stress can stimulate a rapid release of NO via eNOS activation[156] (FIG. 3).

Thus, dysregulation of vascular NO production can occur from chronic cerebral hypoperfusion. The process might unfold as follows: chronic cerebral hypoperfusion leading to CATCH initiates eNOS activation and dysregulation of NO release from endothelium initially in the hippocampus and entorhinal cortex. This action results in increased vascular resistance and viscosity causing microenvironmental hemorheologic and hemodynamic disturbances. This mechanotransduction effect on eNOS activity upregulates NO as a response to reset normal homeostasis and diminish the damage caused by hypoperfusion. Unable to achieve homeostasis, basal NO levels diminish and are unable to (i) regulate normal vascular perfusion, (ii) block granulocyte adherence in blood vessels, and (iii) prevent proinflammatory reactions intraneuronally (FIG. 3). Additionally, low basal levels of NO are unable to maintain endothelial cell conformation, resulting in endothelial cell shape distortions[6] (FIG. 3). Such a phenomenon may explain basement membrane thickening commonly found regionally in Alzheimer brain capillaries. Basement membrane thickening could be a compensatory reaction to increased interendothelial distance created by NO dysregulation.[6] Endothelial cell distortion would also permit mobilization of the powerful vasoconstrictor, endothelin-1 (ET-1),[157] and impair glucose transporter-1 activity, the molecule responsible for glucose transport into brain.

NO appears to directly affect NF-κβ, a transcription factor widely expressed in the nervous system, for the activation of several inflammatory mediators, for example, TNF-α, interferon-β, IL-8, IL-1β, IL-2, and IL-6.[158] Upon NF-κβ activation, in most types of cells, its inhibitor IκBα is phosphorylated and proteolytically degraded.[158] After activation, free NF-κβ dimers are directly translocated into the nucleus where they bind to the promoter regions of target genes and induce transcription required for DNA binding and protein dimerization[158,159] (FIG. 3).

The expression of adhesion molecules on the endothelial surface is mediated by TNF-α-induced NF-κβ activation[160–162] (FIG. 3). NO inhibits NF-κβ transcriptional activation in a variety of cells, including monocytes and endothelial cells.[159,163] When NO is activated by TNF-α, IκBα (the inhibitor of NF-κβ) is no longer stabilized and inflammatory cytokines such as IL-1 and IL-6 are activated in the brain (FIG. 3). Structural microvessel pathology, which is frequently observed in AD brain, results in basement membrane thickening, buckling of the lumen, and distortion of the endothelium (FIG. 3). Such microvessel pathology will alter normal NO release from endothelium, allowing IκBα degradation and, in so doing, preventing downregulation of proinflammatory events via inhibition of NF-κβ.[164]

Thus, it is possible that vascular NO, derived from eNOS, may tonically inhibit NF-κβ under nonstimulated conditions.[165] However, during advanced aging, coupled to a vascular risk factor that further reduces cerebral perfusion, this influence may be lost, allowing for greater sensitivity to NF-κβ activation. Supporting this important hypothesis that associates vascular NO with AD is the finding that TNF-α, in the presence of two NO donors, is unable to stimulate NF-κβ from human endothelial cells, allowing NO to stabilize the NF-κβ inhibitor, IκBα, by preventing its degradation.[164] The binding of NF-κβ to the NF-κβ binding site in the iNOS promoter plays a crucial role in the transcriptional regulation of the iNOS gene.[166] Furthermore, NO donors can directly inhibit the DNA binding activity of NF-κβ.[167] In short, NO derived from eNOS has the ability to downregulate proinflammatory events by inhibiting NF-κβ activation of proinflammatory cytokines.

There are multiple pathologic permutations that can result from vascular NO dysregulation in Alzheimer capillaries, and this brief review can only underline some of the most elemental. What is important to note is that these collective studies indicate that capillary endothelial cell function and release of NO play a critical role in the hemodynamic, humoral, and inflammatory signals to which it is constantly exposed by circulating blood cells. AD therefore appears to develop from an endotheliopathy spurred by CATCH.

Regardless of whether our theoretical proposal is correct or not concerning the trigger of AD being caused by cerebrovascular hypoperfusion leading to CATCH and to NO dysregulation, it is important to point out that we have presented here and elsewhere[168,169] considerable evidence indicating that the pathogenesis of this disorder is rooted in vascular pathology and that, in light of such findings, AD should be reclassified from its present status as a "neurodegenerative" condition to one that identifies this illness as arising from vascular pathology with "neurodegenerative consequences" during advanced aging. To paraphrase Darwin, it would be incredible that all these findings be found false or irrelevant.

We have stated in the past, "The goal of medicine is to provide patients with hope, and when there is no hope to offer understanding." For the first time in the history of this disorder, we have the chance to provide Alzheimer patients with hope instead of well-meaning, but helpless, understanding.

ACKNOWLEDGMENTS

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

REFERENCES

1. DE LA TORRE, J.C. & T. MUSSIVAND. 1993. Can disturbed brain microcirculation cause Alzheimer's disease? Neurol. Res. **15:** 146–153.
2. DE LA TORRE, J.C. 1994. Impaired brain microcirculation may trigger Alzheimer's disease. Neurosci. Behav. Rev. **18:** 397–401.
3. DE LA TORRE, J.C. 1999. Critical threshold cerebral hypoperfusion causes Alzheimer's disease. Acta Neuropathol. **98:** 1–8.

4. DE LA TORRE, J.C. 2000. Critically-attained threshold of cerebral hypoperfusion: the CATCH hypothesis of Alzheimer's pathogenesis. Neurobiol. Aging **21**(2)**:** 331–342.
5. DE LA TORRE, J.C. 1997. Hemodynamic consequences of deformed microvessels in the brain in Alzheimer's disease. Ann. N.Y. Acad. Sci. **826:** 75–91.
6. DE LA TORRE, J.C. & G.B. STEFANO. 2000. Evidence that Alzheimer's disease is a microvascular disorder: role of constitutive nitric oxide. Brain Res. Rev. **34:** 119–136.
7. BRETELER, M.M. 1998. Epidemiological evidence of a connection between Alzheimer's disease and vascular dementia. Neurobiol. Aging **19**(4S)**:** S150.
8. BRETELER, M.M., M.L. BOTS, A. OTT & A. HOFMAN. 1998. Risk factors for vascular disease and dementia. Haemostasis **28:** 167–173.
9. BRETELER, M.M. 2000. Vascular involvement in cognitive decline and dementia: epidemiologic evidence from the Rotterdam Study and the Rotterdam Scan Study. Ann. N.Y. Acad. Sci. **903:** 457–465.
10. BRETELER, M.M. 2000. Vascular risk factors for Alzheimer's disease: an epidemiological study. Neurobiol. Aging **21:** 153–160.
11. OTT, A., R.P. STOLK, A. HOFMAN *et al*. 1996. Association of diabetes mellitus and dementia: the Rotterdam Study. Diabetologia **39:** 1392–1397.
12. OTT, A., R.P. STOLK, A. HOFMAN *et al*. 1999. Diabetes mellitus and the risk of dementia: the Rotterdam Study. Neurology **53:** 1907–1909.
13. BOTS, M.L., F. VAN KOOTEN, F. HAVERKATE *et al*. 1998. Coagulation and fibrinolysis markers and risk of dementia: the Dutch Vascular Factors in Dementia Study. Haemostasis **28:** 216–222.
14. KALMIJN, S., L.J. LAUNER, J. LINDEMANS *et al*. 1999. Total homocysteine and cognitive decline in a community based sample of elderly subjects: the Rotterdam Study. Am. J. Epidemiol. **150:** 283–289.
15. OTT, A., M.M. BRETELER, M.C. DE BRUYNE *et al*. 1997. Atrial fibrillation and dementia in a population-based study: the Rotterdam Study. Stroke **28:** 316–321.
16. OTT, A., A.J. SLOOTER, A. HOFMAN *et al*. 1998. Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: the Rotterdam Study. Lancet **351:** 1840–1843.
17. VAN DUIJN, C.M., L.M. HAVEKES, C. VAN BROECKHOVEN *et al*. 1995. Apolipoprotein E genotype and association between smoking and early onset Alzheimer's disease. Br. Med. J. **310:** 627–631.
18. GRAVES, A.B., C.M. VAN DUIJN, V. CHANDRA *et al*. 1991. Alcohol and tobacco consumption as risk factors for Alzheimer's disease: a collaborative reanalysis of case-controlled studies—EURODEM Risk Factors Research Group. Int. J. Epidemiol. **20:** S48–S57.
19. OTT, A., M.M. BRETELER, F. VAN HARSKAMP *et al*. 1995. Prevalence of Alzheimer's disease and vascular dementia association with education: the Rotterdam Study. Br. Med. J. **310:** 970–973.
20. HOFMAN, A., M.M. BRETELER, M.L. BOTS *et al*. 1997. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. Lancet **349:** 151–154.
21. TYAS, S.L., J. MANFREDA, L.A. STRAIN & P.R. MONTGOMERY. 2001. Risk factors for Alzheimer's disease: a population-based, longitudinal study in Manitoba, Canada. Int. J. Epidemiol. **30:** 590–597.
22. KALMIJN, S. 1997. Dietary fat intake and risk of incident dementia in the Rotterdam Study. Ann. Neurol. **42:** 776–782.
23. DAVIGNON, J., R.E. GREGG & C.F. SING. 1998. Apolipoprotein E polymorphism and atherosclerosis. Atherosclerosis **8:** 1–21.
24. NOTKOLA, I.L., R. SULKAVA, J. PEKKANEN *et al*. 1998. Serum total cholesterol, apolipoprotein E epsilon 4 allele, and Alzheimer's disease. Neuroepidemiology **17:** 14–20.
25. MEYER, J.S., G. RAUCH, R.A. RAUCH & A. HAQUE. 2000. Risk factors for cerebral hypoperfusion, mild cognitive impairment, and dementia. Neurobiol. Aging **21:** 161–169.
26. DEVANAND, D.P., M. SANO, M. TANG *et al*. 1996. Depressed mood and the incidence of Alzheimer's disease in the elderly living in the community. Arch. Gen. Psychiatry **53:** 175–182.
27. GEERLINGS, M.I., R.A. SCHOEVERS, A. BEEKMAN *et al*. 2000. Depression and risk of cognitive decline and Alzheimer's disease: results of two prospective community-based studies in the Netherlands. Br. J. Psychiatry **176:** 568–575.

28. GRAVES, A.B., C.M. VAN DUIJN, V. CHANDRA *et al*. 1991. Alcohol and tobacco consumption as risk factors for Alzheimer's disease: a collaborative reanalysis of case-controlled studies—EURODEM Risk Factors Research Group. Int. J. Epidemiol. **20:** S48–S57.
29. DIAZ-ARRASTIA, R. 1998. Hyperhomocysteinemia: a new risk factor for Alzheimer's disease? Arch. Neurol. **55:** 1–2.
30. SESHADRI, S., A. BEISER, J. SELHUB *et al*. 2002. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N. Engl. J. Med. **346:** 476–483.
31. OHKURA, T., K. ISSE, K. AKAZAWA *et al*. 1994. Evaluation of estrogen treatment in female patients with dementia of the Alzheimer type. Endocr. Rev. **41:** 361–371.
32. WARING, S.C., W.A. ROCCA *et al*. 1999. Postmenopausal estrogen replacement therapy and risk of AD: a population-based study. Neurology **52:** 965–970.
33. AJMANI, R.S., E.J. METTER, R. JAYCUMAR *et al*. 2000. Hemorheological changes during aging associated with cerebral blood flow and impaired cognitive function. Neurobiol. Aging **21:** 257–270.
34. SOLERTE, S.B., E. FERRARI & M. FIORAVANTI. 2000. Hemorheologic changes and overproduction of cytokines in mild to moderate dementia of the Alzheimer's type: adverse effects on cerebrovascular system and therapeutic approach with pentoxifylline. Neurobiol. Aging **21:** 271–282.
35. FIORAVANTI, M., T. RICCIARDI, M. COTTINELLI *et al*. 1998. Hemorheologic alterations and acute-phase reaction are related to recent-onset patients with senile dementia of the Alzheimer's type. Neurobiol. Aging **19**(4S)**:** S246–S247.
36. MORRISON, R.A., A. MCGRATH, G. DAVIDSON *et al*. 1996. Low blood pressure in Down's syndrome: a link with Alzheimer's disease? Hypertension **28:** 569–575.
37. PASSANT, U., S. WARKENTIN & L. GUSTAFSON. 1997. Orthostatic hypotension and low blood pressure in organic dementia: a study of prevalence and related clinical characteristics. Int. J. Geriatr. Psychiatry **12:** 395–403.
38. GUO, Z., M. VIITANEN, L. FRATIGLIONI & B. WINBLAD. 1997. Blood pressure and dementia in the elderly: epidemiologic perspectives. Biomed. Pharmacother. **51:** 68–73.
39. JENDROSKA, K., O.M. HOFFMANN & S. PATT. 1997. Amyloid β peptide and precursor protein (APP) in mild and severe brain ischemia. Ann. N.Y. Acad. Sci. **826:** 401–405.
40. SNOWDON, D.A., L. GREINER, J. MORTIMER *et al*. 1997. Brain infarction and the clinical expression of Alzheimer disease: the Nun Study. JAMA **277:** 813–817.
41. GUO, Z., L.A. CUPPLES, A. KURZ *et al*. 2000. Head injury and the risk of AD in the MIRAGE study. Neurology **54:** 1316–1323.
42. PLASSMAN, B.L., R.J. HAVLIK *et al*. 2000. Documented head injury in early childhood and risk of Alzheimer's disease and other dementias. Neurology **55:** 1158–1166.
43. LYE, T.C. & E.A. SHORES. 2000. Traumatic brain injury as a risk factor for Alzheimer's disease: a review. Neuropsychol. Rev. **10:** 115–129.
44. KILANDER, L., B. ANDREN, H. NYMAN *et al*. 1998. Atrial fibrillation is an independent determinant of low cognitive function: a cross-sectional study in elderly men. Stroke **29:** 1816–1820.
45. DEKLUNDER, G., M. ROUSSEL, J.L. LECROART *et al*. 1998. Microemboli in cerebral circulation and alteration of cognitive abilities in patients with mechanical prosthetic heart valves. Stroke **29:** 1821–1826.
46. AMADUCCI, L.A., A. LIPPI & L. FRATIGLIONI. 1988. What risk factors are known? *In* Etiology of Dementia of Alzheimer's Type, pp. 29–37. Plenum. New York
47. MAXWELL, A.J. 2002. Mechanisms of dysfunction of the nitric oxide pathway in vascular diseases. Nitric Oxide Biol. Chem. **6:** 101–124.
48. KALARIA, R.N. & C. BALLARD. 1999. Overlap between pathology of Alzheimer disease and vascular dementia. Alzheimer Dis. Assoc. Disord. **13**(suppl. 3)**:** S115–S123.
49. SKOOG, I. 1999. Vascular factors in dementia. Alzheimer Dis. Assoc. Disord. **13**(suppl. 3)**:** S106–S114.
50. GROVES, W.C., J. BRANDT, M. STEINBERG *et al*. 2000. Vascular dementia and Alzheimer's disease: is there a difference? A comparison of symptoms by disease duration. J. Neuropsychiatry Clin. Neurosci. **12**(3)**:** 305–315.
51. VILLARDITA, C. 1993. Alzheimer's disease compared with cerebrovascular dementia: neuropsychological similarities and differences. Acta Neurol. Scand. **87:** 299–308.

52. LAUNER, L.J., G.W. ROSS, H. PETROVICH *et al*. 2000. Midlife blood pressure and dementia: the Honolulu-Asia Aging Study. Neurobiol. Aging **21:** 49–55.
53. KIVIPELTO, M., E.L. HELKALA *et al*. 2001. Midlife vascular risk factors and late-life cognitive impairment: a population-based study. Neurology **56:** 1683–1689.
54. KORCZYN, A.D. 2002. Mixed dementia—the most common cause of dementia. Ann. N.Y. Acad. Sci. This volume.
55. BROE, G.A., D.A. GRAYSON, H. CREASEY *et al*. 2000. Anti-inflammatory drugs protect against Alzheimer's disease at low doses. Arch. Neurol. **57:** 1586–1591.
56. LE BARS, P.L., M. KIESER & K. ITIL. 2000. A 26-week analysis of a double-blind, placebo-controlled trial of the ginkgo biloba extract Egb 761 in dementia. Dement. Geriatr. Cogn. Disord. **11:** 230–237.
57. FORSTL, H. 2000. Clinical issues in current drug therapy for dementia. Alzheimer Dis. Assoc. Disord. **14**(suppl. 1)**:** S103–S108.
58. LOSORDO, D.W. & J.M. ISNER. 2001. Estrogen and angiogenesis: a review. Arterioscler. Thromb. Vasc. Biol. **21:** 6–12.
59. OHKURA, T., K. ISSE, K. AKAZAWA *et al*. 1994. Evaluation of estrogen treatment in female patients with dementia of the Alzheimer type. Endocr. J. **41:** 361–371.
60. WARING, S.C., W.A. ROCCA *et al*. 1999. Postmenopausal estrogen replacement therapy and risk of AD: a population-based study. Neurology **52:** 965–970.
61. GROPPA, S.A. 1994. New possibilities in the treatment of patients with Alzheimer's disease. Neurobiol. Aging **15:** S101.
62. BREITNER, J.C., B.A. GAU, K.A. WELSH, *et al*. 1994. Inverse association of anti-inflammatory treatments and Alzheimer's disease: initial results of a co-twin control study. Neurology **44:** 227–232.
63. SANO, M., C. ERNESTO, R.G. THOMAS *et al*. 1997. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease: the Alzheimer's Disease Co-operative Study. N. Engl. J. Med. **336:** 1216–1222.
64. REICHMAN, W.E. 2000. Alzheimer's disease: clinical treatment options. Am. J. Manag. Care **22:** S1125–S1132.
65. PETTEGREW, J.W., J. LEVINE & R.J. MCCLURE. 2000. Acetyl-L-carnitine physical-chemical, metabolic, and therapeutic properties: relevance for its mode of action in Alzheimer's disease and geriatric depression. Mol. Psychiatry **5:** 616–632.
66. POSTIGLIONE, A., A. SORICELLI, U. CICERANO *et al*. 1991. Effect of acute administration of L-acetyl carnitine on cerebral blood flow in patients with chronic cerebral infarct. Pharmacol. Res. **23:** 242–246.
67. IN'T VELD, B.A., A. RUITENBERG, A. HOFMAN *et al*. 2001. Antihypertensive drugs and incidence of dementia: the Rotterdam Study. Neurobiol. Aging **22:** 407–412.
68. JICK, H., G. ZORNBERG, S.S. JICK *et al*. 2000. Statins and the risk of dementia. Lancet **356**(9242)**:** 1627–1631.
69. WOLOZIN, B., W. KELLMAN, P. RUOSSEAU *et al*. 2000. Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Arch. Neurol. **57:** 1439–1443.
70. THOMAS, T. 2000. Monoamine oxidase-β-inhibitors in the treatment of Alzheimer's disease. Neurobiol. Aging **21:** 343–348.
71. BOZOKI, A., B. GIORDANI, J.L. HEIDEBRINK *et al*. 2001. Mild cognitive impairments predict dementia in non-demented elderly patients with memory loss. Arch. Neurol. **58:** 411–416.
72. MORRIS, J.C., M. STORANDT, J.P. MILLER *et al*. 2001. Mild cognitive impairment represents early stage Alzheimer's disease. Arch. Neurol. **58:** 397–405.
73. SHAH, S., E.G. TANGALOS & R. PETERSEN. 2000. Mild cognitive impairment: when is it a precursor of Alzheimer's disease? Geriatrics **55:** 65–68.
74. JOHNSON, K.A., K. JONES, B.L. HOLMAN *et al*. 1998. Preclinical prediction of Alzheimer's disease using SPECT. Neurology **50:** 1563–1571.
75. JOHNSON, K.A. & M.S. ALBERT. Perfusion abnormalities in prodromal Alzheimer's disease. Neurobiol. Aging **21:** 289–292.
76. KOGURE, D., H. MATSUDA, T. OHNISHI *et al*. 2000. Longitudinal evaluation of early Alzheimer's disease using brain perfusion SPECT. J. Nucl. Med. **41:** 1155–1162.

77. OKAMURA, N., M. SHINKAWA, H. ARAI *et al*. 2000. Prediction pf progression in patients with mild cognitive impairment using IMP-SPECT. Nippon Ronen Igakkai Zasshi **37:** 974–978.
78. RODRIGUEZ, G., P. VITALI, P. CALVINI *et al*. 2000. Hippocampal perfusion in mild cognitive impairment. Psychiatry Res. **100:** 65–74.
79. DE SANTI, S., M.J. DE LEON, H. RUSINEK *et al*. 2001. Hippocampal formation glucose metabolism and volume losses in MCI and AD. Neurobiol. Aging **22:** 529–539.
80. ARNAIZ, E., V. JELIC, O. ALMKVIST *et al*. 2001. Impaired cerebral glucose metabolism and cognitive functioning predict deterioration in mild cognitive impairment. Neuroreport **12:** 851–855.
81. DE LEON, M., A. CONVIT, O.T. WOLF *et al*. 2001. 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. U.S.A. **98:** 10966–10971.
82. BOWLER, J.V., M. ELIASZIW *et al*. 1997. Comparative evolution of Alzheimer's disease, vascular dementia, and mixed dementia. Arch. Neurol. **54:** 697–703.
83. RANSMAYR, G. 1998. Difficulties in the clinical diagnosis of vascular dementia and dementia of the Alzheimer type: comparison of clinical classifications. J. Neural Transm. **53:** 79–90.
84. AGUERO-TORRES, H. & B. WINBLAD. 2000. Alzheimer's disease and vascular dementia: some points of confluence. Ann. N.Y. Acad. Sci. **903:** 547–552.
85. WALLIN, A. 1998. The overlap between Alzheimer's disease and vascular dementia: the role of white matter changes. Dement. Geriatr. Cogn. Disord. **1:** 30–35.
86. SCHELTENS, P. & E.S. KORF. 2000. Contribution of neuroimaging in the diagnosis of Alzheimer's disease and other dementias. Curr. Opin. Neurol. **13:** 391–396.
87. BARBER, R., P. SCHELTENS, A. GHOLKAR *et al*. 1999. White matter lesions on magnetic resonance imaging in dementia with Lewy bodies, Alzheimer's disease, vascular dementia, and normal aging. J. Neurol. Neurosurg. Psychiatry **67:** 66–72.
88. TARKOWSKI, E., K. BLENNOW, A. WALLIN & A. TARKOWSKI. 1999. Intracerebral production of tumor necrosis factor-alpha, a local neuroprotective agent, in Alzheimer's disease and vascular dementia. J. Clin. Immunol. **19:** 223–230.
89. PARNETTI, L., G.P. REBOLDI & V. GALLAI. 2000. Cerebrospinal fluid pyruvate levels in Alzheimer's disease and vascular dementia. Neurology **54:** 735–737.
90. CARANTONI, M., G. ZULIANI, M. MUNARI *et al*. 2000. Alzheimer disease and vascular dementia: relationship with fasting glucose and insulin levels. Dement. Geriatr. Cogn. Disord. **11:** 176–180.
91. ELLIS, R.J., J.M. OLICHNEY, L. THAL *et al*. 1996. Cerebral amyloid angiopathy in the brains of patients with Alzheimer's disease: the CERAD experience—part XV. Neurology **46:** 1592–1596.
92. ROSENGREN, L.E., J.E. KARLSSON, M. SJOGREN *et al*. 1999. Neurofilament protein levels in CSF are increased in dementia. Neurology **52:** 1090–1093.
93. RODRIGUEZ, M.T., A.M. CALELLA, S. SILVA & E. MUNNA. 2000. Apolipoprotein E and intronic polymorphism of presenilin 1 and alpha-1-antichymotrypsin in Alzheimer's disease and vascular dementia. Dement. Geriatr. Cogn. Disord. **11:** 239–244.
94. ZHANG, J.G., J.G. YANG, Z. LIN *et al*. 2001. Apolipoprotein E epsilon 4 allele is a risk factor for late-onset Alzheimer's disease and vascular dementia in Han Chinese. Int. J. Geriatr. Psychiatry **16:** 438–439.
95. BONAREK, M., P. BARBERGER-GATEAU *et al*. 2000. Relationship between cholesterol, apolipoprotein E polymorphism, and dementia: a cross-sectional analysis from the PAQUID Study. Neuroepidemiology **19:** 141–148.
96. WEHR, H., T. PARNOWSKI, S. PUZYNSKI *et al*. 2000. Apolipoprotein E genotype and lipid lipoprotein levels in dementia. Dement. Geriatr. Cogn. Disord. **11:** 70–73.
97. KALARIA, R.N., H.D. LEWIS, N. THOMAS & S. SHEARMAN. 1999. Brain Aβ42 and Aβ40 concentrations in multi-infarct dementia and Alzheimer's disease. Soc. Neurosci. Abstr. **23:** 1114.
98. BALLARD, C., J. O'BRIEN, C.M. MORRIS *et al*. 2001. The progression of cognitive impairment in dementia with Lewy bodies, vascular dementia, and Alzheimer's disease. Int. J. Geriatr. Psychiatry **16:** 499–503.

99. HOLMES, C., N. CAIRNS, P. LANTOS & A. MANN. 1999. Validity of current clinical criteria for Alzheimer's disease, vascular dementia, and dementia with Lewy bodies. Br. J. Psychiatry **174:** 45–50.
100. O'BRIEN, J.T., S. PALING, R. BARBER *et al*. 2001. Progressive brain atrophy on serial MRI in dementia with Lewy bodies, Alzheimer's, and vascular dementia. Neurology **56:** 1386–1388.
101. MORRIS, J.C. 2000. The nosology of dementia. Neurol. Clin. **18:** 773–788.
102. DICKSON, D.W. 2001. Neuropathology of Alzheimer's disease and other dementias. Clin. Geriatr. Med. **17:** 209–228.
103. ERKINJUNTTI, T. 2001. Clinical deficits of Alzheimer's disease with cerebrovascular disease and probable VaD. Int. J. Clin. Pract. **120:** 14–23.
104. WENTZEL, C., S. DARVESH, C. MACKNIGHT *et al*. 2000. Inter-rater reliability of the diagnosis of vascular cognitive impairment at a memory clinic. Neuroepidemiology **19:** 186–193.
105. ROMAN, G. 2001. Diagnosis of vascular dementia and Alzheimer's disease. Int. J. Clin. Pract. **120:** 9–13.
106. CHUI, H.C., W. MACK, J.E. JACKSON *et al*. 2000. Clinical criteria for the diagnosis of vascular dementia: a multicenter study of comparability and interrater reliability. Arch. Neurol. **57:** 191–196.
107. TARKOWSKI, E., K. BLENNOW, A. WALLIN & A. TARKOWSKI. 1999. Intracerebral production of tumor necrosis factor-alpha, a local neuroprotective agent, in Alzheimer's disease and vascular dementia. J. Clin. Immunol. **19:** 223–230.
108. DE JONG, G.I., R.A.I. DE VOS, E. JANSSEN-STEUR & P.G. LUITEN. 1997. Cerebrovascular hypoperfusion: a risk factor for Alzheimer's disease? Animal model and postmortem human studies. Ann. N.Y. Acad. Sci. **826:** 56–74.
109. HATANPÄÄ, K. 1996. Neuronal activity and early neurofibrillary tangles in Alzheimer's disease. Ann. Neurol. **40:** 411–420.
110. DUARA, R., W.W. BARKER, J. CHANG & F. YOSHII. 1992. Viability of neocortical function shown in behavioral activation state PET studies in Alzheimer's disease. J. Cereb. Blood Flow Metab. **12:** 927–934.
111. DAVIS, D.G., F.A. SCHMITT, D. WEKSTEIN & W.R. MARKESBERY. 1999. Alzheimer neuropatholoic alterations in aged cognitively normal subjects. J. Neuropathol. Exp. Neurol. **58:** 376–388.
112. BUEE, L., P.R. HOF, C. BOURAS *et al*. 1994. Pathological alterations of the cerebral microvasculature in Alzheimer's disease and related demented disorders. Acta Neuropathol. **87:** 469–480.
113. JONES, A.M., N. KENNEDY, J. HANSON & G.W. FENTON. 1997. A study in adults with Down's syndrome using 99Tc(m)-HMPAO SPET. Nucl. Med. Commun. **18:** 662–667.
114. KAO, C.H., P.Y. WANG, S.J. WANG *et al*. 1993. Regional cerebral blood flow of Alzheimer's disease-like pattern in young patients with Down's syndrome detected by 99Tcm-HMPAO brain SPECT. Nucl. Med. Commun. **14:** 47–51.
115. NUNOMURA, A., G. PERRY *et al*. 2000. Neuronal oxidative stress precedes amyloid-beta deposition in Down syndrome. J. Neuropathol. Exp. Neurol. **59:** 1011–1017.
116. DE LA TORRE, J.C., A. CADA *et al*. 1997. Reduced cytochrome oxidase and memory dysfunction after chronic brain ischemia in aged rats. Neurosci. Lett. **223:** 165–168.
117. ABDOLLAHIAN, N.P., A. CADA, F. GONZALEZ-LIMA & J.C. DE LA TORRE. 1998. Cytochrome oxidase: a predictive marker of neurodegeneration. *In* Cytochrome Oxidase in Neuronal Metabolism and Alzheimer's Disease, pp. 233–261. Plenum. New York.
118. TANAKA, K., N. WADA & N. OGAWA. 2000. Chronic cerebral hypoperfusion induces transient reversible monoaminergic changes in the rat brain. Neurochem. Res. **25:** 313–320.
119. OUCHI, Y., H. TSUKADA, T. KAKIUCHI *et al*. 1998. Changes in cerebral blood flow and postsynaptic muscarinic activity in rats with bilateral carotid artery ligation. J. Nucl. Med. **39:** 198–202.
120. OTORI, T., T. KATSUMATA, Y. KATAYAMA & A. TERASHI. 1997. Measurement of regional cerebral blood flow and glucose utilization in rat brain under chronic hypoperfusion conditions following bilateral carotid artery occlusion. Nippon Ika Daigaku Zasshi **64:** 428–439.

121. TSUCHIYA, M., K. SAKO, S. YURA & Y. YONEMASU. 1993. Local cerebral glucose utilization following acute and chronic bilateral carotid artery ligation in Wistar rats: relation to changes in local cerebral blood flow. Exp. Brain Res. **95:** 1–7.
122. DE LA TORRE, J.C., T. FORTIN *et al*. 1992. Chronic cerebrovascular insufficiency induces dementia-like deficits in aged rats. Brain Res. **582:** 186–195.
123. PAPPAS, B.A., C. DAVIDSON, S. BENNETT *et al*. 1997. Chronic ischemia: memory impairment and neural pathology in the rat. Ann. N.Y. Acad. Sci. **826:** 498–501.
124. IHARA, M., H. TOMIMOTO, M. KINOSHITA *et al*. 2001. Chronic cerebral hypoperfusion induces MMP-2, but not MMP-9 expression in the microglia and vascular endothelium of white matter. J. Cereb. Blood Flow Metab. **21:** 828–834.
125. TANAKA, K., N. WADA, K. HORI *et al*. 1998. Chronic cerebral hypoperfusion disrupts discriminative behavior in acquired-learning rats. J. Neurosci. Methods **84:** 63–68.
126. NI, J.W., H. OHTA, K. MATSUMOTO & H. WATANABE. 1994. Progressive cognitive impairment following chronic cerebral hypoperfusion induced by permanent occlusion of bilateral carotid arteries in rats. Brain Res. **653:** 231–236.
127. BURMESTER, T., B. WEICH, S. REINHARDT & T. HANKELN. 2000. A vertebrate globin expressed in the brain. Nature **407**(6803)**:** 461–462.
128. DE LA TORRE, J.C. 2000. Impaired cerebromicrovascular perfusion: summary of evidence in support of its causality in Alzheimer's disease. Ann. N.Y. Acad. Sci. **924:** 136–152.
129. DE LA TORRE, J.C. 2000. Cerebral perfusion, capillary degeneration, and development of Alzheimer's disease. Alzheimer Dis. Assoc. Disord. **14:** S72–S81.
130. MARTIN, A.J., K.J. FRISTON, J.G. COLEBATCH & R. FRACKOWIAK. 1991. Decreases in regional cerebral blood flow with normal aging. J. Cereb. Blood Flow Metab. **11:** 684–689.
131. SMALL, S.A., W. TSAI *et al*. 2002. Imaging hippocampal function across the human life span: is memory decline normal or not? Ann. Neurol. **51:** 290–295.
132. ERECINSKA, M. & I. SILVER. 1989. ATP and brain function. J. Cereb. Blood Flow Metab. **9:** 2–12.
133. LEHMANN, M., C.G. GOTTFRIES & B. REGLAND. 1999. Identification of cognitive impairment in the elderly: homocysteine is an early marker. Dement. Geriatr. Cogn. Dis. **10:** 12–20.
134. MEIER-RUGE, W. & C. BERTONI-FREDDARI. 1996. The significance of glucose turnover in the brain in the pathogenic mechanisms of Alzheimer's disease. Rev. Neurosci. **7:** 1–19.
135. PASCHEN, W., K.C. GISSEL, T. LINDEN *et al*. 1998. Activation of gadd153 expression through transient cerebral ischemia: evidence that ischemia causes endoplasmic reticulum dysfunction. Brain Res. Mol. Brain Res. **18:** 115–122.
136. PASCHEN, W. & J. DOUTHEIL. 1999. Disturbances of the functioning of endoplasmic reticulum: a key mechanism underlying neuronal cell injury? J. Cereb. Blood Flow Metab. **19:** 1–18.
137. ABE, K., M. AOKI, J. KAWAGOE *et al*. 1995. Ischemic delayed neuronal death: a mitochondrial hypothesis. Stroke **26:** 1478–1489.
138. KAKIMURA, J., Y. KITAMURA & T. TANIGUCHI. 2001. Bip/GRP78-induced production of cytokines and uptake of amyloid-β(1–42) peptide in microglia. Biochem. Biophys. Res. Commun. **28:** 6–10.
139. SCHELLER, R.H. & Z.W. HALL. 1992. Chemical messengers at synapses. *In* Molecular Neurobiology, pp. 119–147. Sinauer Associates. Sunderland, MA.
140. GREENFIELD, J.P., J. TSAI, G.K. GOURAS *et al*. 1999. Endoplasmic reticulum and trans-Golgi network generate distinct populations of Alzheimer β-amyloid peptides. Proc. Natl. Acad. Sci. U.S.A. **96:** 742–747.
141. HARTMANN, T., S.C. BIEGER *et al*. 1997. Distinct sites of intracellular production of Alzheimer's disease Aβ40/42 amyloid peptides. Nat. Med. **3:** 1016–1020.
142. PIKE, C.J., M.J. OVERMAN & C. COTMAN. 1995. Amino-terminal deletions enhance aggregation of β-amyloid peptides *in vitro*. J. Biol. Chem. **270:** 23895–23898.
143. CHEN, Y., S. WEII, Z. MOURELATOS *et al*. 1998. The fragmented neuronal Golgi apparatus in ALS includes the trans-Golgi-network: functional implications. Acta Neuropathol. **95:** 245–253.
144. HAMMERSCHLAG, R. & G.C. STONE. 1982. Membrane delivery by fast axonal transport. Trends Neurosci. **5:** 12–15.

145. STIEBER, A., Z. MOURELATOS & N.K. GONATAS. 1996. In Alzheimer's disease the Golgi apparatus of a population of neurons without neurofibrillary tangles is fragmented and atrophic. Am. J. Pathol. **148:** 415–426.
146. STIEBER, A., Y. CHEN, S. WEI *et al*. 1998. The fragmented neuronal Golgi apparatus in amyotrophic lateral sclerosis includes the trans-Golgi-network: functional implications. Acta Neuropathol. **95:** 245–253.
147. MUFSON, E.J., J.S. KROIN, T.J. SENDERA & T. SOBREVIELA. 1999. Distribution and retrograde transport of trophic factors in the central nervous system: functional implications for the treatment of neurodegenerative disease. Prog. Neurobiol. **57:** 451–484.
148. LUTH, H.J., M. HOLZER, U. GARTNER *et al*. 2001. Expression of endothelial and inducible NOS-isoforms is increased in Alzheimer's disease, in APP23 transgenic mice, and after experimental brain lesion in rat: evidence for an induction by amyloid pathology. Brain Res. **913:** 57–67.
149. LEE, T.J. 2000. Nitric oxide and cerebral vascular function. J. Biomed. Sci. **7:** 16–26.
150. HUANG, Z., P.L. HUANG, N. PANAHIAN *et al*. 1994. Effects of cerebral ischemia in mice deficient of neuronal nitric oxide synthase. Science **265:** 1883–1885.
151. KUBES, P. & D. GRANGER. 1992. Nitric oxide modulates microvascular permeability. Am. J. Physiol. **262:** H611–H615.
152. KUBES, P., S. KANWAR & X.F. NIU. 1993. Nitric oxide synthesis inhibition induces leukocyte adhesion via superoxide and mast cells. FASEB J. **7:** 1293–1299.
153. NIU, X.F., C.W. SMITH & P. KUBES. 1995. Intracellular oxidative stress induced by nitric oxide synthesis inhibition increases endothelial cell adhesion to neutrophils. Circ. Res. **74:** 1133–1140.
154. NAPOLI, C. & L.J. IGNARRO. 2001. Nitric oxide and atherosclerosis. Nitric Oxide **5:** 88–97.
155. SCHINI–KERTH, V.B. 1999. Vascular biosynthesis of nitric oxide: effect on hemostasis and fibrinolysis. Transfus. Clin. Biol. **6:** 355–363.
156. MALEK, A.M., S. IZUMO & S.L. ALPER. 1999. Modulation by pathophysiological stimuli of the shear stress–induced up-regulation of endothelial nitric oxide synthase expression in endothelial cells. Neurosurgery **45:** 334–345.
157. CHEN, Y., R. MCCARRON, J. BEMBRY *et al*. 1999. Nitric oxide modulates endothelin-1 induced Ca^{2+} mobilization and cytoskeletal F-actin filaments in human cerebromicrovascular endothelial cells. J. Cereb. Blood Flow Metab. **19:** 133–138.
158. BLACKWELL, T.S., T.R. BLACKWELL *et al*. 1996. *In vivo* antioxidant treatment suppresses nuclear factor-kappa B activation and neutrophilic lung inflammation. J. Immunol. **157:** 1630–1637.
159. SIEBENLIST, U., G. FRANZOSO & K. BROWN. 1994. Structure, regulation, and function of NF-kappa B. Annu. Rev. Cell Biol. **10:** 405–455.
160. LEDEBUR, H.C. & T.P. PARKS. 1995. Transcriptional regulation of the intercellular adhesion molecule-1 gene by inflammatory cytokines in human endothelial cells: essential roles of a variant NF-kappa B site and p65 homodimers. J. Biol. Chem. **270:** 933–943.
161. CHEN, C.C., C.L. ROSENBLOOM, D.C. ANDERSON & A.M. MANNING. 1995. Selective inhibition of E-selectin, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1 expression by inhibitors of I-kappa B-alpha phosphorylation. J. Immunol. **155:** 3538–3545.
162. READ, M.A., M.Z. WHITLEY, A.J. WILLIAMS & T. COLLINS. 1994. NF-kappa B and I kappa B alpha: an inducible regulatory system in endothelial activation. J. Exp. Med. **179:** 503–512.
163. SHIN, W.S., Y.H. HONG, H.B. PENG *et al*. 1996. Nitric oxide attenuates vascular smooth muscle cell activation by interferon-gamma: the role of constitutive NF-kappa B activity. J. Biol. Chem. **71:** 11317–11324.
164. PENG, H.B., P. LIBBY & J.K. LIAO. 1995. Induction and stabilization of I kappa B alpha by nitric oxide mediate inhibition of NF-kappa B. J. Biol. Chem. **270:** 14214–14219.
165. WELTERS, I., C. FIMIANI., T.V. BILFINGER & G.B. STEFANO. 2000. NF-kB, nitric oxide, and opiate signaling. Med. Hypotheses **54:** 263–268.
166. XIE, Q. & C. NATHAN. 1994. The high-output nitric oxide pathway: role and regulation. J. Leukocyte Biol. **56:** 576–582.

167. MATTHEWS, J.R., C.H. BOTTING, M. PANICO *et al*. 1996. Inhibition of NF-kappa B DNA binding by nitric oxide. Nucleic Acids Res. **24:** 2236–2242.
168. DE LA TORRE, J.C. 2002. Alzheimer disease as a vascular disorder: nosological evidence. Stroke **33:** 1152–1162.
169. DE LA TORRE, J.C. 1997. Hemodynamics of deformed microvessels in Alzheimer's disease brain. Ann. N.Y. Acad. Sci. **826:** 75–91.