Review Article

Alzheimer's Disease, Amnestic Mild Cognitive Impairment, and Age-Associated Memory Impairment: Current Understanding and Progress Toward Integrative Prevention

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Abstract

Alzheimer's disease (AD) is the most common form of dementia. AD initially targets memory and progressively destroys the mind. The brain atrophies as the neocortex suffers neuronal, synaptic, and dendritic losses, and the "hallmark" amyloid plaques and neurofibrillary tangles proliferate. Pharmacological management, at best, is palliative and transiently effective, with marked adverse effects. Certain nutrients intrinsic to human biochemistry (orthomolecules) match or exceed pharmacological drug benefits in double-blind, randomized, controlled trials (RCT), with superior safety. Early intervention is feasible because its heritability is typically minimal and pathological deterioration is detectable years prior to diagnosis. The syndrome amnestic mild cognitive impairment (aMCI) exhibits AD pathology and to date has frustrated attempts at intervention. The condition age-associated memory impairment (AAMI) is a nonpathological extreme of normal brain aging, but with less severe cognitive impairment than aMCI. AAMI is a feasible target for early intervention against AD, beginning with the modifiable AD risk factors – smoking, hypertension, homocysteine, type 2 diabetes, insulin resistance, and obesity. Stress reduction, avoidance of toxins, and mental and physical exercise are important aspects of prevention. The diet should emphasize omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA); flavonoids and other antioxidant nutrients; and B vitamins, especially folate, B_6, and B_{12}. Dietary supplementation is best focused on those proven from RCT: the phospholipids phosphatidylserine (PS) and glycerophosphocholine (GPC), the energy nutrient acetyl-L-carnitine, vitamins C and E, and other antioxidants. A comprehensive integrative strategy initiated early in cognitive decline is the most pragmatic approach to controlling progression to Alzheimer's disease. (*Altern Med Rev* 2008;13(2):85-115)

Introduction

Alzheimer's disease (AD) is a devastating disease that takes away the very essence of a person – their sense of self. AD, the most prevalent form of dementia, accounts for 50-70 percent of dementia cases[1] and significantly impacts patients, families, caregivers, communities, and society as a whole. Current medical management of AD is ineffectual, with no cure on the horizon.

Conventional medicine has little to offer for Alzheimer's disease. The five pharmaceutical drugs approved in the United States as primary AD therapies can slow the progression of some symptoms, but generally only for 6-12 months;[2] half of all patients may show no improvement. A number of nutrients studied in double-blind, randomized clinical trials (RCTs) have shown significant efficacy and safety. Nevertheless, the AD diagnosis comes at such an advanced stage of neurodegeneration, and the disease progression is so unremitting, that chances for its eventual effective management seem remote.

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Despite this pessimistic scenario there are reasons for optimism. Intensive research is in progress on every aspect of the disease. The main emphasis is on early intervention. Techniques have recently become available that accurately detect a likely prodrome of AD, called amnestic mild cognitive impairment (aMCI), which is considered pathological. Another condition, age-associated memory impairment (AAMI), is a non-pathological condition that also carries heightened risk for progression to AD. AAMI, an extreme of normal aging, is less severe than aMCI and consequently offers more promise for successful early intervention.

This review discusses the current medical management of AD, efforts at early detection and intervention of aMCI, and the possibilities for primary prevention of AAMI. The many established and putative risk factors for AD are catalogued. A comprehensive, multimodal, early intervention strategy appears to be the most pragmatic approach to controlling Alzheimer's disease and takes advantage of the best features of integrative medicine.

What is Alzheimer's? The Disease and its Progression

Historical Perspective

In 1901, the German psychiatrist and neuropathologist Aloysius Alzheimer first observed a 51-year-old patient, Auguste D., who was plagued by symptoms that did not fit any existing diagnosis: rapidly failing memory, confusion, disorientation, trouble expressing her thoughts, and unfounded suspicions about her family and the hospital staff. His patient progressed inexorably, one day saying to Dr. Alzheimer, "I have lost myself."[3]

Alzheimer performed an autopsy on Auguste D. upon her death, after four years of steady decline that left her bedridden and mute. Autopsy revealed a dramatically shrunken brain but no evidence of atherosclerosis. Nissl silver staining histology of the brain yielded widespread dead and dying cells and two microscopic deposits that have become hallmarks of the disease: "plaques" (amyloid plaque) and "tangles" (neurofibrillary tangles or NFT), located in the upper cortical layers. The deeper hippocampus and entorhinal region were not sampled.[3]

Subsequently, Alzheimer described a second case, that of Johann F., whose brain differed in that it lacked NFT – a "plaque-only" case. Such cases remain part of the modern disease type.[4] These two initial cases, published as "presenile dementia" by Alzheimer, later became labeled Alzheimer's disease by Kraepelin.[4] Miraculously, histological slides of both cases have survived to the present, and modern re-examinations confirm Alzheimer's original findings.[4]

Framework for the Alzheimer's Disease Diagnosis

The term "dementia" refers to a group of disorders that cause cognitive decline as a result of death or damage to brain cells. By definition, dementia causes a decline in at least two of four essential cognitive functions: (1) memory; (2) ability to speak or understand language; (3) capacity to plan, make sound judgments, and carry out complex tasks; and (4) ability to process and interpret visual information. The decline must be severe enough to interfere with day-to-day life.[1,5]

The typical Alzheimer's symptom pattern begins with memory loss for recent events (short-term memory).[1,5] Pathologically, amyloid plaques and neurofibrillary tangles are still its hallmarks. Since these cannot be definitively identified until autopsy, the Alzheimer's diagnosis remains one of exclusion.

The most widely accepted diagnostic criteria for probable AD were developed by the U.S. National Institute of Neurological and Communicative Disorders and Stroke and by the Alzheimer's Disease and Related Disorders Association joint-working group.[6] These specify that dementia be established by clinical examination and confirmed by neuropsychological testing. The dementia should involve multiple, progressive cognitive deficits in older persons in the absence of other medical, neurological, or psychiatric conditions that might account for the deficits.

The *U.S. Diagnostic and Statistical Manual*, 4th Edition, Text Revision (DSM-IV-TR)[5] offers a stepwise diagnosis of AD. The first step in the progression is memory loss. Second, at least one other cognitive deficit occurs, including aphasia (language deterioration), apraxia (motor difficulties), agnosia (failure to recognize objects despite intact sensory capacity), or a disturbance in executive functioning. These cognitive deficits

must be sufficiently severe to cause impairment in occupational or social performance (e.g., going to school, working, shopping, dressing, bathing, handling finances, and other activities of daily living), and must represent a decline from a previous level of functioning.

Disturbances in executive functioning are common in AD. The DSM-IV-TR defines executive functioning as "the ability to think abstractly and to plan, initiate, sequence, monitor, and stop complex behavior."[5] The individual has trouble coping with novel tasks and avoids situations that require the processing of new and complex information. Tests for executive function include asking the individual to count to 10, recite the alphabet, subtract serial 7s, state as many animals as possible in one minute, or draw a continuous line consisting of alternating m's and n's. Often the individual or the individual's caregivers report difficulty with ability to work, plan daily activities, budget, and so on.

The DSM-IV-TR emphasizes that, to reach a diagnosis of probable Alzheimer's disease, various other dementia etiologies must be ruled out. Delirium can cause memory impairment, but typically is less stable and long-lasting than dementia. Severe memory impairment without other cognitive involvement qualifies as an amnestic disorder but not as dementia. The diagnosis of vascular dementia is attributable to circulatory dysfunction or disease. HIV infection, encephalitis, and stroke can cause dementia due to other general medical conditions. Substance intoxication or withdrawal can lead to substance-induced persisting dementia. When these are ruled out, dementia of the Alzheimer's type can be considered, provided the history includes gradual onset and continuing decline.[5]

Prevalence of Alzheimer's Disease

The Alzheimer's Association of the United States in its 2007 *Facts and Figures* report[1] estimates 5.1 million Alzheimer's cases. Of these, only about 200,000 (4%) occur in people younger than age 65 – designated as early-onset Alzheimer's disease, known to be familial, and variously related to gene mutations. The remaining 4.9 million cases (96 percent) occur at or over age 65 and are labeled late-onset AD.[1] Prevalence in Europe likely exceeds 4.8 million.[7] Worldwide prevalence of AD is estimated at 18 million in 2008.[8]

Of Americans over age 65, 13 percent – one in eight – have AD; over age 85, as many as 50 percent are afflicted. Every 72 seconds someone in the United States develops Alzheimer's disease. The Association predicts this number will swell as the "baby boomer" generation approaches age 65. AD is the fifth leading cause of death for people age 65 and older.[1]

Of the 4.9 million cases of late-onset or "sporadic" AD (idiopathic; cause or causes unknown), by age group:[1]

- Age 65-74: 300,000 (2 percent)
- Age 75-84: 2,400,000 (19 percent)
- Age 85+: 2,200,000 (42 percent)

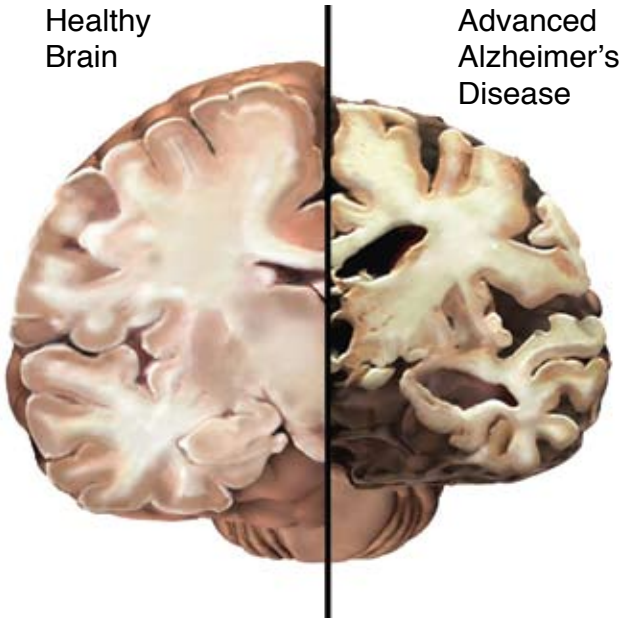
To date, late-onset AD shows no substantial gene linkage, with the notable exception of apolipoprotein E4 gene (ApoE4), which is firmly implicated as an AD risk factor. Both heterozygous and homozygous individuals are at higher risk for AD, with homozygotes having the highest risk. Still, of ApoE4/4 individuals, half do not develop AD.

The institutional cost of caring for AD patients is three times that for people without dementia.[1] In the United States more than 70 percent of Alzheimer's patients are cared for at home, and the average patient lives 8-20 years after being diagnosed. The Alzheimer's Association data suggest that for the year 2005 (most recent available), total cost to the national government, states, the healthcare sector, and lost productivity approached $300 billion.[1]

The Pathophysiology of Alzheimer's Disease

At autopsy the Alzheimer's brain displays widespread changes, including atrophy (Figure 1).[9-11] The folds of the brain's outer layer (gyri) are shrunken, and the grooves (sulci) are noticeably widened. The ventricles, chambers within the brain containing cerebrospinal fluid, are noticeably enlarged. Brain mass is reduced up to one-third, attributable to significant loss of nerve cells, synapses, and dendrites. Most of this circuit dropout occurs in the neocortex.[9] By comparison, the healthy brain suffers only modest loss of mass during aging.[11]

Figure 1. The Healthy Brain (left) and the Alzheimer's Brain (right)



This is a gross comparison of slices through the middle of the brain between the ears. Note the markedly smaller size of the Alzheimer's brain. The folds and grooves of the outer layer are atrophied and the ventricles are larger.

From: the Alzheimer's Association, © 2007 Alzheimer's Association.org, www.alz.org. Illustration by Stacy Jannis. Used with permission.

Neocortical Degeneration

In humans the neocortex makes up most of the cortex. Approximately six cells thick, it is the outermost cortical zone.[9] This zone encompasses the highest order association areas that manage the most sophisticated cognitive processes. Amyloid becomes deposited in the extracellular spaces within nerve tissue and in the blood vessel walls.[10] This causes endothelial damage resulting in cerebral amyloid angiopathy that can rupture arteries and arterioles in the cortex. Such hemorrhages are often the cause of death for the AD patient.[10]

Because the inner areas of the cortex typically remain relatively intact, the senses are relatively preserved. However, as the limbic structures – the hippocampus, entorhinal cortex (EC), and amygdala – progressively become involved, the individual loses emotional capabilities.

Hippocampus and Entorhinal Cortex

The hippocampus and EC work in tandem for learning and memory. The EC is neocortical and is one of the first areas to show abnormalities, consistent with memory loss being one of the earliest symptoms of AD. The hippocampus can sustain extreme damage; by the time of death an Alzheimer's patient may have lost virtually all the hippocampal CA1 cells crucial for memory formation.[11]

Amygdala

The amygdala is a nucleus located relatively deep in the cortex beneath the temporal lobe. It operates in coordination with the EC and hippocampus and is associated with emotional screening of information reaching the brain. As this zone deteriorates, so also does the ability to appreciate the emotional significance of new experience.[9] Several other small "nuclei" deeper in the brain also typically become afflicted, as discussed below.[9]

Nucleus Basalis of Meynert (NBM)

A tiny nucleus on the rostral-most portion of the reticular formation, the NBM uses acetylcholine (ACh) as its main chemical transmitter and has widespread projections to the cortex. The NBM's function is unclear, but according to Norden its degeneration is closely linked with the emergence of dementia.[9]

Nucleus Locus Coeruleus (NLC)

The NLC is a tiny nucleus in the reticular formation, a zone that utilizes norepinephrine as its main neurotransmitter.[9] Like the NBM, it too has direct projections to the cortex. The NLC has many functions in

the regulation of blood flow, extraction of oxygen and glucose from the blood, and in selective attention. The NLC also plays a major role in sleep-wake cycles.

Raphe Nuclei

The raphe nuclei are groups of serotonergic neurons in the reticular formation, extending from the medulla to the midbrain.[9] They also have massive projections to the cortex. Current evidence indicates the raphe nuclei contribute to mood management.

Blood-Brain Barrier (BBB)

In some AD patients the BBB becomes permeable,[12] allowing greater access of toxins or other harmful agents to the brain tissue. BBB failure has been linked to accelerated disease progression and suggested as an explanation for encephalitis linked to the ill-fated Alzheimer's vaccine.[12,13]

The Cell-Level Progression of Alzheimer's Disease

The brain zones affected in AD have significantly lower nerve cell, dendrite branches, and synapse densities. Throughout the tissue there is debris from damaged or dead cells, extracellular deposits of amyloid, and previous intracellular tangles that can retain ghostly outlines after the cells disintegrate.[9] Although nondementia brains also exhibit amyloid and tangles (especially with aging and the presence of the ApoE4 gene), the AD brain has quantitatively more plaques and tangles.

The neurofibrillary tangles arise within individual neurons as depositions of abnormally twisted filaments. The tau protein normally is linearly organized into microtubules that give scaffolding to the nerve cells. In AD the tau proteins are excessively phosphorylated, causing them to form abnormally twisted filaments aggregated in tangles. Braak et al developed a system to rate the extent and severity of tangles.[14] The system ranges from zero at baseline through six abnormal stages. The first stage has been observed in people as young as age 20.[15]

It is believed tangles most often appear in the EC, near the base of the skull, and later spread to the hippocampus, then to the neocortex, which can take 50 years or longer. Although more dense distribution of tangles (Braak stages V-VI) is usually thought to denote more severe Alzheimer's symptomatology, the findings from the Nun Study suggest this correlation does not always hold.[15]

The Nun Study was initiated in 1986 by Snowdon, who obtained the cooperation of the Catholic Order School Sisters of Notre Dame to do ongoing functional assessments, blood sampling, and other monitoring until the nuns died, then have access to their brains for study. This has become a landmark study and has yielded a wealth of information about brain aging, risk factors for AD (or lack thereof), and correlates of Alzheimer's disease with cognitive capacity, lifestyle, and diet. The nuns in this study did not experience AD as a consequence of aging; only 3 of 13 who surpassed age 100 had severe AD pathology.[15] Their spirituality, strong positive community life, and near-pristine lifestyle all seem to have contributed to a much lower incidence of AD than the general population. Snowdon noted the nuns who had Alzheimer's symptoms at death also had micro-infarcts and other circulatory abnormalities in the brain tissue.[15]

The nuns did not show a strong correlation of NFT distribution with symptomatology because, if infarcts were not apparent, they were cognitively intact despite very dense NFT.[15] For the general population, however, postmortem examination, other histology, non-invasive metabolic imaging techniques, and high-resolution MRI all correlate with the histologic progression of Alzheimer's gleaned from Braak staging. In 2008, a European cooperative group of 25 experts concluded Braak staging is 50-percent reproducible when the tangles are mild (stages I-II), rising to 91 percent at stages V-VI.[16] NFT distributions can now be imaged using positron emission tomography (PET) scans.[17]

Amyloid plaques are aggregates of beta-amyloid (AB42), a protein found in plaques in the normal, healthy brain. AB42 is a large protein remnant from the snipping of a larger protein (called amyloid precursor or APP) by the enzyme gamma-secretase. AD tissue has more AB42, and in AD the single AB42 units (monomers) are abnormally sticky, both factors thought to promote abnormal amyloid plaque formation.[10] Amyloid can also be accurately imaged using PET scans, with a radio-labeled agonist for AB42.[18]

Inflammation in the AD Cortex

The brain demonstrates immune capability; at least 12 percent of the cells of the central nervous system are immune cells (mostly macrophages, known in the brain as microglia, and astrocytes).[19] In the AD brain, activated microglia and astrocytes are concentrated in the vicinity of amyloid plaques. Axons and dendrites in the immediate surroundings are often structurally abnormal – a pattern suggestive of chronic inflammation.

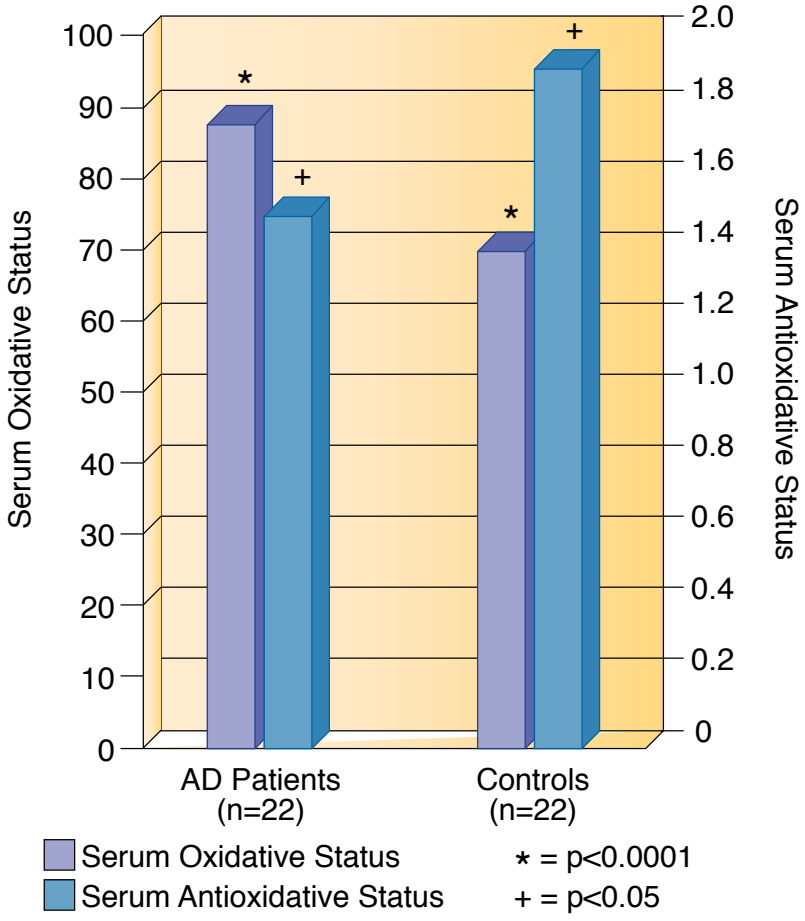
Evidence suggests AD involves low-level chronic inflammation of the brain's gray matter.[19] This inflammation is likely stimulated by AB42 buildup and is regulated by the resident microglia and astrocytes, both of which can be anti-inflammatory or proinflammatory depending on activation state. Experimental evidence suggests AB42 directly damages nerve cells even as it activates the microglia and the astrocyes.[19] Details of the inflammatory progression in AD are not yet resolved, but may be more atypical than first thought, especially since non-steroidal anti-inflammatory drugs (NSAIDs) have not produced consistent benefit in controlled trials.

Oxidative Stress

Oxidative stress is clearly evident in AD.[20] Numerous oxidative stress biomarkers are elevated in the blood and brain. The brain zones demonstrating the highest levels of oxidative stress are typically the areas most structurally affected by disease: hippocampus, amygdala, parietal cortex, and other neocortical zones.[20,21]

Oxidative stress is a relative increase in the ratio of free radicals to antioxidants.[21,22] Brain tissue is especially vulnerable to oxidative attack due to its relatively low antioxidant capacity, high consumption of oxygen, high content of polyunsaturated fatty acids, and high content of redox-active transition metals such as iron.[20]

Figure 2. Serum Oxidative and Antioxidative Status of Alzheimer's Patients versus Healthy Controls



AD oxidative status was significantly greater versus controls, and antioxidative capacity significantly poorer than controls.

Adapted from: van Rensburg SJ, van Zyl JM, Potocnik FCV, et al. The effect of stress on the antioxidative potential of serum: implications for Alzheimer's disease. *Metab Brain Dis* 2006;21: 171-179. Used with permission from Springer Publishing.

Other tissues of AD patients also can manifest oxidative stress. Van Rensburg et al found the blood of AD patients demonstrates increased oxidative stress and abnormally poor antioxidant status compared to healthy controls (Figure 2).[22]

Reactive oxygen species (ROS) and reactive nitrogen species (RNS), along with reactive aliphatic and aromatic carbon compounds (RCS) and many other substances with free radical character, can react with proteins, lipids, carbohydrates, DNA, and RNA, damaging or destroying cells.[23] Alzheimer's brain tissue displays ample amounts of damage to these molecular types.[20,22]

Using a new technique of redox proteomics, Butterfield et al are cataloguing specific oxidatively damaged proteins in AD brain tissue.[20] They identified 18 such damaged proteins involved in cholinergic and other neurotransmitter action, synaptic function and memory trace formation, cell structure, pH regulation, and energetics. Seven are energy-related enzymes: creatine kinase, alpha-enolase, lactate dehydrogenase (LDH), triosephosphate isomerase (TPI), phosphoglycerate mutase I (PGMI), and glyceraldehyde-3-phosphate dehydrogenase (GAPDH).

The presence of several glycolytic enzymes on this oxidative hit list (alpha-enolase, LDH, TPI, PGMI, and GAPDH) is especially significant because the brain is heavily dependent on glucose as its energy source. Glycolysis impairment would disrupt energetics throughout the AD brain. Butterfield's group ascertained that beagle dogs are a good model of human AB42-induced brain oxidation, and by feeding antioxidants to beagles have succeeded in protecting some proteins from oxidative damage as their brains accumulate amyloid.[24]

Mitochondrial Compromise

Even worse than glycolytic compromise in the brain is compromise of oxygen-dependent energy generation – oxidative phosphorylation (OXPHOS), as occurs in the mitochondria.[25,26] The mitochondria are the energy-generating organelles of every human cell.[25] Mitochondria are key players in oxidative stress phenomena because they generate more than 90 percent of the cell's endogenous oxidant species.[26] Mitochondrial degeneration has been suggested to contribute to Alzheimer's disease.[27] Mitochondrial energetic enzymes are markedly impaired in AD.[28] Mitochondrial damage likely occurs early in AD; mitochondrial DNA shows abnormally elevated oxidation products in the temporal, parietal, and frontal lobes of the AD brain.[20,29]

Butterfield's group identified two mitochondrial proteins as oxidation-sensitive – ATP synthase and voltage-dependent anion channel protein (VDAC).[20] VDAC is essential for moving ATP out of the mitochondria. ATP synthase is pivotal to ATP production as the end-stage of OXPHOS.[30] Compromise to ATP production capacity inside the mitochondria likely contributes to the energetic abnormalities of AD seen on PET imaging and to findings of altered glucose metabolism and tolerance in AD patients.[20,31]

The Amyloid Cascade Hypothesis of Alzheimer's causation is based on the presence of extracellular amyloid deposition and to a lesser extent on intracellular NFT accumulation. It emphasizes amyloid-driven inflammation as the primary initiating factor.[32] Amyloid may also stimulate oxidative stress, particularly since it has become clear that small, water-soluble amyloid oligomers permeate the brain.[20,23,33] Of the two amyloid beta-peptides, AB42, the more toxic amyloid molecular species, has been found inside the mitochondria of AD neurons[34] and is likely disruptive to mitochondrial function.

Considering that mitochondrial dysfunction reportedly enhances AB42 accumulation in the neuron cytoplasm, thereby enhancing neuronal vulnerability,[35] these phenomena might contribute to a "vicious cycle" involving amyloid deposition, mitochondrial failure, energetic failure, functional neuronal impairment, and cell death.

Early Energetic Decline

PET imaging can assess local cerebral glucose metabolism (lCGM) with increasing precision. Early PET studies have found neocortical higher-association areas in the AD brain demonstrated markedly decreased glucose consumption, particularly the frontal and temporal cortex.[20,36,37] The primary visual and sensorimotor cortex, basal ganglia, and cerebellum are relatively spared.[36] Automated analysis of the lCGM neocortical patterns from PET scans can distinguish between controls and AD patients with 93-percent sensitivity and 93-percent specificity. Even very mild dementia (Mini-Mental State Exam (MMSE) score 24 or higher) can be distinguished at 84-percent sensitivity and 93-percent specificity.[36]

The metabolic impairment seen with PET correlates well with autopsy studies, which reveal decreased activity of pyruvate dehydrogenase (PDH) and the Krebs cycle enzyme alpha-ketoglutarate dehydrogenase (KGD) in the frontal, temporal and parietal cortex.[20] Complex IV of the mitochondrial OXPHOS chain is also consistently decreased in the AD brain.[38]

Evidence strongly suggests oxidative stress and mitochondrial compromise both contribute to AD. Whether these are primary initiating insults or whether one or both arise secondary to previous insults is unclear. Findings that brain tissue from MCI patients displays abnormally elevated protein damage suggest one or both dysfunctional states could be primary contributors to AD.[20,23]

Current Medical Management of Alzheimer's Disease

To treat cognitive symptoms, the U.S. Food and Drug Administration (FDA) has approved five drugs that affect the activities of two chemical neurotransmitter systems – acetylcholine and glutamate.

Cholinesterase Inhibitor Drugs

Acetylcholine is a neurotransmitter centrally involved in learning, memory, judgment, attention, and concentration. Normally, ACh is transiently released at the presynaptic terminal, stimulates receptors on the postsynaptic terminal, and is then rapidly broken down by the enzyme cholinesterase to terminate the synaptic signal.[25] Cholinesterase inhibitor (CI) drugs prevent the breakdown of ACh, thereby conserving ACh at the synaptic junctions. FDA-approved CI drugs are tacrine, donepezil, galantamine, and rivastigmine.[2]

Tacrine was the first CI drug, approved in 1993 (brand name Cognex®), but it is currently rarely prescribed because of liver toxicity and other major adverse effects.[39] Its immediate successor, approved for all stages of AD, donepezil (Aricept®), is less toxic but still has appreciable adverse effects.[40] Galantamine (Razadyne®) and rivastigmine (Exelon®) are approved for mild-to-moderate AD.[2] Donepezil appears to be the most effective and best tolerated, although all four CI drugs have marginal clinical utility.[2,39]

Areas of the brain that depend predominantly on cholinergic circuitry are generally the first and most severely damaged by AD.[2] The mechanism involved in cholinesterase inhibitor drugs involves blocking breakdown of ACh, thus elevating ACh levels at the cholinergic synapses and (in theory) compensating for loss of cholinergic circuits.[41] However, in clinical trials and practice, cognitive benefits of CI drugs are minimal; more than half the subjects show no measurable improvement. Furthermore, the window of efficacy averages six months to one year; benefits fade as brain deterioration worsens.

CI drugs seem to be well tolerated, with the exception of tacrine. When prescribed by experienced physicians under recommended guidelines, side effects can include nausea, vomiting, loss of appetite, and increased frequency of bowel movements. Combining CI drugs does not heighten efficacy and could increase adverse effects.[2]

Idebenone is a synthetic, low-molecular-weight derivative of ubiquinone (coenzyme Q10). A 2002 RCT compared idebenone to tacrine in patients with mild-to-moderate probable AD.[42] Patients (n=203) were randomized to either 360 mg idebenone (n=104) or 160 mg tacrine (n=99) daily for 60 weeks. An Efficacy Index Score (EIS) integrated scores for cognitive function, activities of daily living, and global function. The idebenone patients showed higher EIS benefit than the tacrine patients. The significance of this trial is doubtful, however, due to the poor compliance rate; after the 60-week treatment period only 29 percent of idebenone patients and nine percent of tacrine patients were still on the drug.

Glutamate Enhancement

Glutamate is another prevalent brain neurotransmitter. When released presynaptically, glutamate is essential to learning and memory via facilitation of n-methyl-d-aspartate (NMDA) receptors that allow small influxes of calcium into stimulated nerve cells. Limited increase of ionic calcium inside the cell triggers changes required for long-term potentiation and the related processes that culminate in formation of a memory trace.[25] Although the glutamate neurotransmitter system is delicately balanced, excess glutamate can over-stimulate NMDA receptors, allowing too much calcium into the nerve cells, causing functional disruption and cell death. Pharmacological NMDA blockers down-regulate NMDA receptors and render them less sensitive to overstimulation.[2]

Memantine (Namenda®) is an NMDA-receptor antagonist. Although memantine has shown no apparent benefits in mild-to-moderate AD, it is FDA approved for moderate-to-severe AD.[2] A 2007 meta-analysis found limited but statistically significant benefits for cognition, behavior, and activities of daily living over a six-month trial period.[43] Memantine's side effects include headache, constipation, confusion, and dizziness.

Nutrients for Alzheimer's Disease: Orthomolecules

In 1968, two-time Nobel laureate, Linus Pauling, PhD, conceived of the treatment of disease or the correction of metabolic imbalances by substances naturally part of human biochemistry – what he termed *molecules orthodox* to the body, *orthomolecules*.[44] Pauling predicted, because of intrinsic biochemical value and evolutionary intimacy with living systems, orthomolecules would be effective and safe for long-term use.

This concept has been confirmed by the clinical experience of nutritionally oriented physicians. Direct validation at the biochemical level came with the report by Ames et al in 2002,[26] mostly from experiments with cultured cells, that at least 50 human genetic diseases involving defective enzymes could be remedied by increasing available concentrations of a nutrient component of the coenzyme; the authors acknowledged Pauling's contribution.

RCTs have demonstrated the efficacy of certain orthomolecules for AD; each is summarized in the section that follows. To ensure the scientific quality of the clinical research and for the sake of brevity, the review includes only double-blind trials.

Phosphatidylserine (PS)

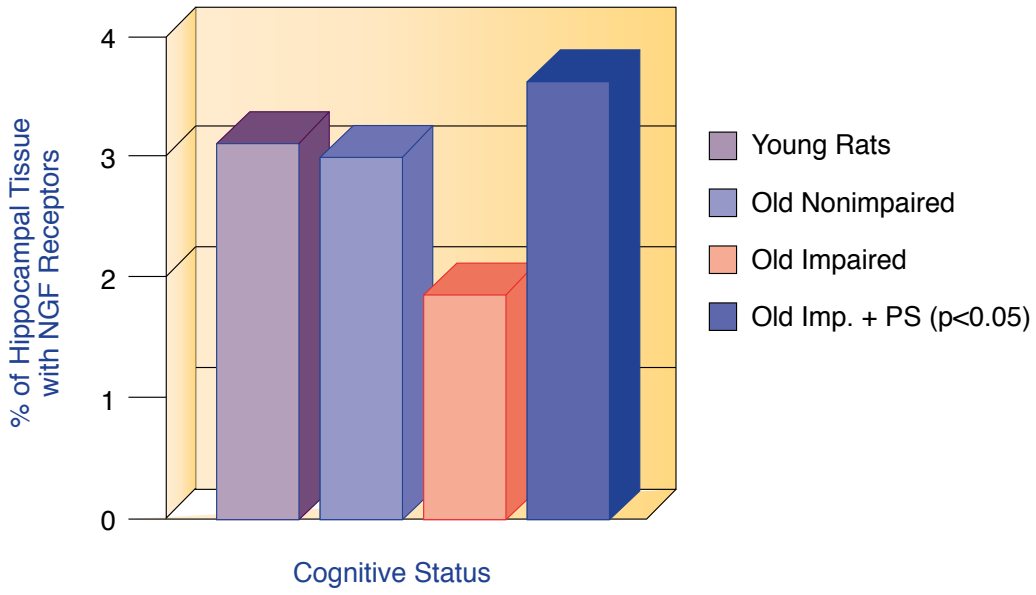
Phospholipids are molecular building blocks for cell membranes, the dynamic sites of most life processes.[25] PS is a vital phospholipid found most concentrated in brain tissue. PS supports many cellular functions particularly important to the brain, including mitochondrial membrane integrity for energy production, neuronal membrane electrical depolarization, presynaptic neurotransmitter release, postsynaptic receptor activity, and activation of protein kinase C (PKC) – an enzyme complex crucial for neuronal signal transduction and memory trace formation.[45] PKC dysfunction is one of the earliest changes noted in AD and is being investigated as a target for drug development.[46]

PS has been found effective for AD in six double-blind trials.[45] At daily doses of 200-300 mg for up to six months, PS consistently improved clinical global impression and activities of daily living. In more mild cases, PS improved orientation, concentration, learning, and memory for names, locations, and recent events. In the largest trial, involving 425 patients with moderate-to-severe cognitive loss, PS significantly improved memory, learning, motivation, socialization, and general "adaptability to the environment."[47]

Animal experiments suggest PS has a trophic (growth supportive) effect on the brain. Compared to younger rats, older rats normally have fewer and smaller brain neurons and decreased cell surface-receptor density for nerve growth factor (NGF). These receptors mediate the actions of NGF to enhance neuronal differentiation and other aspects of neuroplasticity. As rats age, they show declines in NGF-receptor density in the cerebellum, hippocampus, and other brain zones. When dosed with PS, older rats retain more and larger brain neurons along with higher NGF-receptor density. In addition, when older rats are subjected to maze tests, a subpopulation that normally tests significantly more impaired than the average are appropriately labeled "old impaired" rats in contrast to simply "old rats." This impaired subgroup shows the most improvement in cognition and NGF-receptor density when dosed with PS (Figure 3A).[48]

PS and most other phospholipids have fatty acids naturally incorporated in their "parent" molecular structure and position fatty acids in the membrane lipid bilayer.[25] The more fluid the bilayer, the more efficiently it functions. The most fluidizing fatty acids are the omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). A marine-source omega-3 PS containing DHA and EPA recently became available as a dietary supplement.

Figure 3A. Phosphatidylserine: One of Three Orthomolecules that Help Conserve NGF-Receptor Density in the Aging Rat Brain



Adapted from: Nunzi M, Guidolin D, Petrelli L, et al. In: Bazan NG, ed. *Neurobiology of Essential Fatty Acids*. New York: Plenum Press; 1992;393-398. Used with permission from Springer.

Glycerophosphocholine (GPC, alpha-GPC, Choline Alphoscerate, Choline Alfoscerate)

Also a vital phospholipid orthomolecule, GPC differs from PS in being water-soluble and is therefore located in the cytoplasm rather than within the cell membrane. GPC attains high concentrations in some tissues, protecting against osmotic shock and urea buildup.[49]

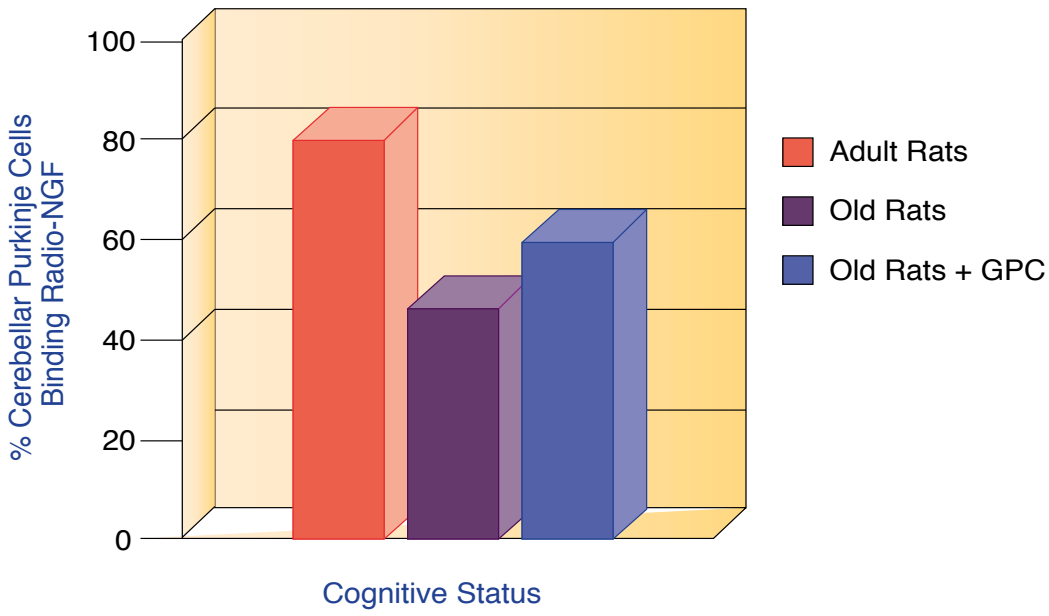
GPC is a cholinergic agonist and supports ACh homeostasis.[50] Following oral dosing with GPC, brain choline levels are markedly elevated within two hours.[50] GPC raises blood choline with a sustained-release pattern, also elevating brain choline, a necessary precursor for biosynthesis of ACh. Besides typically being the first chemical transmitter to become dysfunctional in AD, ACh is ubiquitously distributed throughout the body and not limited to neurons.[41]

GPC demonstrates benefit in AD patients for orientation, attention, memory, language, and mood.[51] In a large, double-blind RCT involving 261 patients, GPC at 1,200 mg/day for six months significantly benefited memory and other cognitive measures.[52] A meta-analysis found GPC offered longer-lasting benefit for Alzheimer's disease compared with donepezil.[53]

GPC is also a neuroprotectant, as determined from a number of animal experiments. The nucleus basalis of Meynert is a cholinergic zone that tends to atrophy early in AD. In rats, oral GPC protected both the NBM and its cholinergic projections to the forebrain cortex and hippocampus from chemically-induced toxin damage.[51,54]

Similar to PS, GPC helps conserve nerve growth factor receptors in aging rats (Figure 3B).[55] Oral GPC protected against this decline in the hippocampus, a brain zone highly dependent on NGF and most active in producing new neurons from stem cells.[56]

Figure 3B. Glycerophosphocholine: One of Three Orthomolecules that Help Conserve NGF-Receptor Density in the Aging Rat Brain



Adapted from: Vega JA, Cavallotti C, Del Valle ME, et al. Nerve growth factor receptor immunoreactivity in the cerebellar cortex of aged rats: effect of choline alfoscerate treatment. *Mech Ageing Dev* 1993;69:119-127. Used with permission from Elsevier.

Acetyl-L-Carnitine (ALC)

ALC, the acetyl ester of the amino acid carnitine, is important for energetics in the brain and other tissues. ALC transports fatty acids from the cell cytoplasm into the mitochondria where they provide substrate for ATP generation via oxidative phosphorylation. ALC, subjected to numerous double-blind trials for AD, has shown limited but measurable effectiveness.

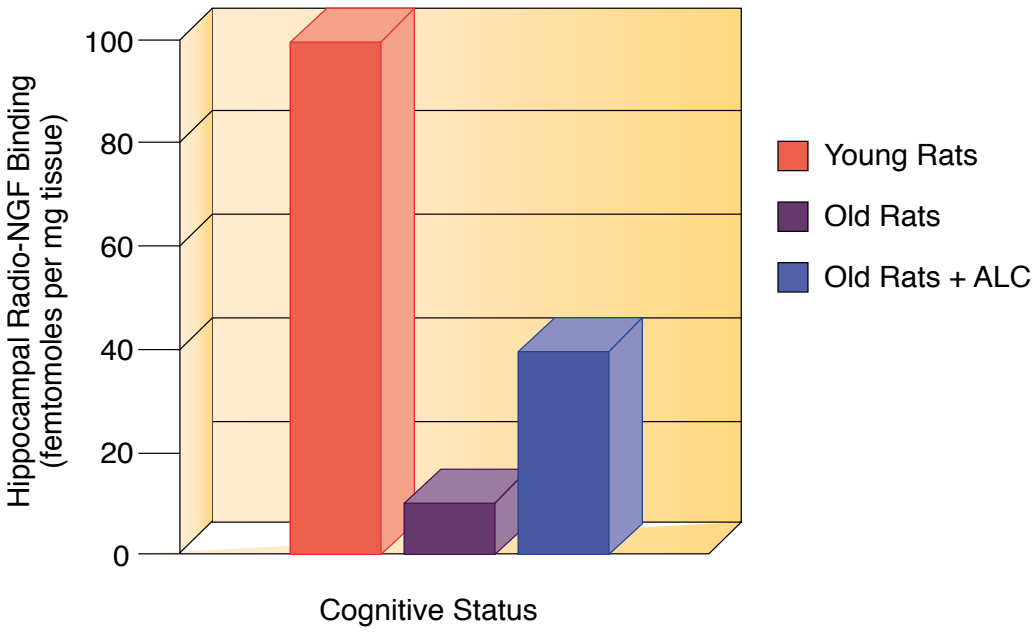
In a 2003 meta-analysis by Montgomery et al that examined double-blind, placebo-controlled trials of at least three-month duration, ALC showed significant benefit over placebo.[57] Daily intakes of ALC of 1.5-3.0 g were well tolerated.

As with PS and GPC, ALC conserves NGF-receptor density in the aging rat brain, partially restoring a youthful receptor profile (Figure 3C).[58]

Omega-3 Fatty Acids

Epidemiological studies indicate relatively high intakes of DHA and EPA are linked to lower risk of dementia incidence or progression, and that better DHA and EPA status correlates with slower cognitive decline over time. The 1997 Rotterdam Study, tracking 5,386 participants age 55 or older for an average of 2.1 years, found a significant link between high fish consumption and lowered Alzheimer's disease risk (RR=0.3; 95% CI=0.1-0.9).[59] A community study in Chicago followed 815 residents ages 65-94 for an average 3.9 years and found consumption of one fish meal weekly can decrease the risk of AD by 60 percent compared to individuals who rarely or never eat fish (RR=0.4; 95% CI=0.2-0.9).[60] Total omega-3 intake and DHA intake, but not EPA intake alone, were significantly associated with decreased AD risk.

Figure 3C. Acetyl-L-Carnitine: One of Three Orthomolecules that Help Conserve NGF-Receptor Density in the Aging Rat Brain



Adapted from: Angelucci L, Ramacci MT, Taglialatela G, et al. Nerve growth factor binding in aged rat central nervous system: effect of acetyl-L-carnitine. *J Neurosci Res* 1988;20:491-496. Used with permission from Wiley-Liss, Inc.

Epidemiological studies can be more reliable when tissue biomarkers are available. One such study at Tufts University measured DHA in plasma phospholipids, specifically as DHA incorporated into phosphatidylcholine (PC-DHA). A cohort of 1,188 elderly Americans (average age 75) was analyzed at baseline and 10 years later.[61] Individuals in the lower half of DHA levels at baseline had a 67-percent greater risk of developing AD within the subsequent 10-year period compared to those with DHA levels in the upper half ($p<0.05$). The correlation of low plasma DHA with AD was confirmed in a Canadian study.[62] An Irish group analyzed serum cholesteryl-DHA and -EPA esters and found both abnormally low in AD subjects.[63]

Only one double-blind, prospective RCT of omega-3 DHA and EPA for treatment of AD has been published.[64] Patients (n=174) received either 1.7 g DHA and 0.6 g EPA daily or a placebo for six months, after which all received the DHA/EPA supplements for six more months. No significant difference was found for the large-group comparisons, but in a subgroup with less severe cognitive dysfunction (MMSE score >27 points), receiving DHA and EPA was associated with a significantly slower decline.

In 2007 this group reported specifically on the neuropsychiatric outcomes of the above Alzheimer's trial.[65] The researchers noted significant improvement of agitation in ApoE4 carriers, and improvement of depression in non-ApoE4 carriers.

Many clinical studies suggest higher intake of DHA and EPA protects against AD risk factors cardiovascular dysfunction, insulin resistance, and systemic inflammation.[59,66,67] The extensive clinical research on omega-3 benefits for the brain was recently reviewed in this journal.[67]

Alternative Medicine Review Volume 13, Number 2 2008

Cold-water fish are the best dietary sources of DHA and EPA. Land-based foods providing shorter-chain omega-3s are less useful because enzymatic conversion to long-chain DHA and EPA is limited, even in healthy people.[67] However, great care must be exercised in sourcing fish because of the risks of contamination by heavy metals and organic pollutants. The expanding availability of DHA and EPA in supplements, eggs, beverages, and other staple foodstuffs now makes it possible to ingest the recommended amounts for adequate nutritional status (in excess of 1 g per day total DHA+EPA).

Omega-6 Essential Fatty Acids

Horrobin et al analyzed red blood cells (RBCs) from 36 AD patients for omega-3 and -6 essential fatty acids and found both were abnormally low.[68] Interestingly, the omega-3 levels were within normal range in plasma, but only 60-70 percent of normal in RBCs.

All 36 patients entered a double-blind, randomized, placebo-controlled trial. One patient group received evening primrose oil (EPO) containing linoleic acid (18:2, omega-6) and gamma-linolenic acid (18:3, omega-6); the exact daily intakes were not provided. To protect against oxidation, the EPO group also received antioxidants vitamin E, selenium, and zinc (intakes unspecified). The placebo group received identical-appearing capsules with antioxidants only. After 20 weeks, the EPO group showed significant improvement on six of eight cognitive tests; the placebo group significantly improved on three of eight tests. The EPO group showed significant improvements in the Hamilton Depression Rating, the Colored Progressive Matrices Test, and the Graded Naming Test compared to the placebo group.

Vitamin E

When the first double-blind RCT of vitamin E for AD was published in the *New England Journal of Medicine* it caused a sensation. This trial was conducted by the Alzheimer's Disease Cooperative Study (ADCS; a consortium of North American AD researchers) at several prestigious American academic centers. A total of 341 patients with moderate AD were randomized to placebo, selegiline, vitamin E, or vitamin E plus selegiline for two years.[69] Vitamin E at a high daily intake (2,000 IU) was found to delay disease progression by seven months and was slightly more beneficial than selegiline.

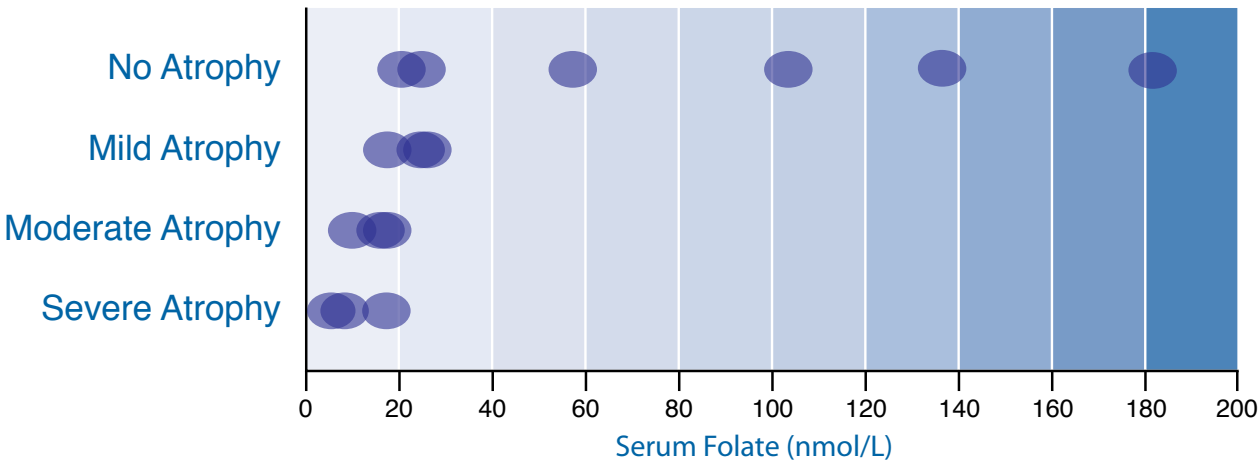
Following on the enthusiastic response to success in this trial, the ADCS organized another, larger double-blind RCT of vitamin E.[70] Subjects (n=769) with amnestic mild cognitive impairment were randomized to either 2,000 IU vitamin E, 10 mg donepezil, or placebo for three years. Vitamin E failed to show benefit.

The form of vitamin E used for these two trials was DL-alpha-tocopherol, the racemic commercial isomer of one of the four tocopherols that have vitamin E activity. Vitamin E is actually a combination of several tocopherols. Recent findings suggest alpha-tocopherol may not be the most representative vitamin E for humans because our foods actually contain more gamma-tocopherol,[71] which demonstrates greater anti-inflammatory activity than alpha-tocopherol.[72] The Chicago Health and Aging Project found increased vitamin E intake (from the diet but not from supplements) correlated with lowered AD risk.[73] Future trials with vitamin E might more appropriately include a mixed-tocopherol supplement.

Increasing evidence suggests nutrients regulate gene activity. New gene chip technology demonstrates vitamin E deficiency can have a strong impact on gene expression in the hippocampus, a key area afflicted by AD. Rota et al used Affymetrix gene chip technology, capable of recording as many as 7,000 genes on a single chip.[74] Rats were fed a diet lacking in vitamin E for nine months. The hippocampus was removed and the genes extracted, then hybridized onto the gene chip (one chip per animal). Vitamin E deficiency was found to down-regulate 948 genes; among which were genes for growth hormone, thyroid hormones, insulin-like growth factor I, NGF, melatonin, dopaminergic neurotransmission, and clearance of advanced glycation end products (AGEs). In particular, vitamin E deficiency strongly down-regulated genes coding for proteins related to clearance of beta-amyloid.

In vivo, vitamin E operates with endogenous antioxidant enzymes and other nutrient antioxidants against oxidative challenge.[75] For example, vitamin E in lipid cell membranes complements vitamin C in the cytoplasm and other water phases. Alzheimer's patients tend to have low serum levels of vitamins E and C, but

Figure 4. The Nun Study: Degrees of Atrophy of the Neocortex, Plotted against Baseline Blood Folate Levels



From: Snowdon DA, Tully CL, Smith CD, et al. Serum folate and the severity of atrophy of the neocortex in Alzheimer disease: findings from the Nun Study. *Am J Clin Nutr* 2000;71:993-998.

this could be related to poor eating habits associated with the disease.[76] Prospective epidemiological studies are more reliable assessments of relationships between vitamin deficiencies and AD. In the Rotterdam Study, individuals who reported higher intakes of vitamins C and E at baseline had lower incidence of AD.[77] The Cache County Study found an association between incidence of AD and intake of both vitamins C and E as dietary supplements, but not with either vitamin alone.[78]

The National Institute on Aging is currently recruiting for a trial on vitamin E plus selenium for AD. In this trial (as has been the case in previous studies), vitamin E is being provided only as alpha-tocopherol, although abundant evidence favors also including gamma-tocopherol. Based on previous research, a better study design would have included vitamin C, selenium, and possibly other antioxidant nutrients with vitamin E. Combination therapy (several nutrients or nutrients plus conventional medications) may offer greater potential to slow or substantially improve quality of life in AD.

Citicoline

Citicoline (cytidine diphosphate choline, cytidine diphosphocholine, CDP-choline) is an energy-activated form of choline – choline linked to cytidine by a diphosphate bridge. It is an intermediate in the biosynthesis of phosphatidylcholine.[53]

Citicoline has been tested for Alzheimer's disease in two double-blind, placebo-controlled trials. The first involved 30 patients with mild-to-moderate AD treated with 1,000 mg oral citicoline daily for three months.[79] Although the overall results showed differences between the citicoline and placebo groups, these did not reach statistical significance.

The second double-blind trial compared citicoline with posatirelin (L-pyro-2-aminoadipyl-L-leucil-L-prolinamide, a synthetic tripeptide) or vitamin C (all administered intramuscularly once daily) in 222 AD outpatients for three months.[80] Posatirelin was superior to citicoline and ascorbic acid on the Gottfries-Brane-Steen (GBS) dementia rating scale. Posatirelin scored significantly superior to both on intellectual impairment, impaired orientation and memory, impaired attention and motivation, activities of daily living, and motor impairment.

A 2005 meta-analysis by the Cochrane group assessed citicoline for the treatment of cognitive, emotional, and behavioral deficits associated with chronic cerebral disorders in the elderly.[81] The reviewers concluded there was some benefit on memory function and behavior. They suggested future clinical trials should extend longer and focus on vascular-related cognitive impairment.

Folic Acid

Although the essentiality of folic acid for neural tube formation in the developing fetus is well established, the Nun Study illuminated folate's pivotal importance in the adult brain.[15,82]

Snowdon et al found a strong association between low blood folate and severity of atrophy in the neocortex on routine blood samples (Figure 4).

Vitamin B_{12}

Vitamin B_{12} deficiency is common in AD patients. Miller reviewed correlation between B_{12} deficiency and increased AD.[83] B_{12} deficiency often occurs concurrently with folate deficiency. In a longitudinal study that followed 370 non-demented subjects for three years, individuals with poor vitamin B_{12} and folate status had double the risk for developing AD.[84]

A double-blind RCT was conducted in Taiwan with 89 mild-to-moderate AD patients.[85] The patients were prescribed a CI drug, then were randomized to receive either a placebo or a B_{12}-multivitamin supplement (500 mcg methylcobalamin, 1,000 mcg folic acid, 5 mg vitamin B_6, other vitamins and iron (amounts unspecified)) for 26 weeks. No statistically significant differences were found between groups, either in cognition or activities of daily living, although blood homocysteine (HCy) levels were significantly reduced in the test group compared to the placebo group.

Vitamins B_6 and B_{12} and folate are cofactors for enzymes that recycle or otherwise deplete HCy.[83] The Mediterranean diet, which is relatively high in these nutrients, has been linked to lowered incidence of AD.[86] Elderly individuals who followed the Mediterranean diet were found to have a 40-percent lower AD risk.[86] The Mediterranean diet also may lower mortality in patients with established AD.[87]

Thiamine

Thiamine (vitamin B_1) is important for glucose metabolism, which is known to decline early in AD; its deficiency can cause irreversible cognitive impairment. Thiamine was used at high doses (3-8 g daily) in three double-blind trials that altogether included fewer than 50 subjects.[88,89] The reported outcomes were inconclusive, partly due to poor disclosure of trial details.

Botanicals for Alzheimer's Disease

Ginkgo Biloba Extracts (GBE)

Standardized leaf extracts of *Ginkgo biloba* (GBE) are the most exhaustively tested botanicals for AD and other dementias. Ginkgo is usually standardized to contain 24-percent flavone glycosides and six-percent terpene lactones (24/6) by weight.

GBE trials specifically for AD are limited. A 1998 meta-analysis by Oken and Storzbach identified four randomized, double-blind, placebo-controlled trials, which totaled 212 subjects given GBE and 212 given placebo. Overall the meta-analysis found a small but statistically significant effect – a three-percent improvement on the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog).[90]

In 2002, LeBars et al reported a re-analysis of the AD patients from an earlier double-blind RCT that included other dementias.[91] In this trial 120 mg EGb 761, a 24/6 preparation, was used daily for one year. For AD patients least severely afflicted at baseline (>23 MMSE), significant improvements were seen over placebo on the ADAS-Cog scale (1.7 points) and on the caregiver's Geriatric Evaluation by Relative's Rating Instrument (GERRI) scale (0.09 points). For those patients moderately afflicted (MMSE <24), the ADAS-Cog improved by 2.5 points and the GERRI did not significantly improve. For patients most severely afflicted at baseline (MMSE <15), those taking EGb 761 deteriorated significantly less than placebo on the ADAS-Cog and GERRI scales. LeBars' group concluded EGb 761 improved AD patients with mild or moderate cognitive impairment and stabilized or slowed the decline of those most severely afflicted.

In 2003, LeBars published another analysis of the data, this time subgrouping AD patients according to neuropsychological profiles.[92] Patients with "right AD" (primarily visual-constructional impairment) may have benefited more from EGb 761 than those with "left AD" (primarily verbal deficits). In the "right AD" group improvements on ADAS-Cog and GERRI were minimal.

In a 2007 Ukrainian double-blind RCT, EGb 761 for 22 weeks significantly improved neuropsychiatric symptoms and activities of daily living in mild or moderate stage AD patients.[93]

GBE dosages in RCTs for AD ranged from 120-240 mg daily for 3-12 months.[90-94] The relatively limited brain efficacy of GBE preparations may be related to poor bioavailability. A proprietary preparation of GBE combined with phosphatidylcholine has demonstrated superior bioavailability over GBE alone.[95]

Although standardized *Ginkgo biloba* extracts have demonstrated few adverse effects, two case reports linking GBE to brain micro-hemorrhages constitute cause for concern.[96] In a 2006 RCT, 50 healthy male subjects received either 500 mg acetylsalicyclic acid (ASA; aspirin) or 500 mg ASA plus 240 mg EGb 761 daily for seven days.[97] Bleeding time was prolonged by ASA as expected, but ASA plus EGB 761 did not further prolong bleeding time. Platelet aggregation was inhibited almost identically by ASA and by ASA plus EGb 761. The researchers concluded safety of EGb 761 was demonstrated in this trial.

In a U.S. RCT, 78 healthy older adults (ages 65-84) received a mixed dietary supplement providing 160 mg GBE, 68 mg gotu kola, and 180 mg DHA daily for four months. Platelet function testing demonstrated no adverse effect from the supplement.[98]

GBE has also been directly compared to a cholinesterase inhibitor – donepezil. In a double-blind RCT, 60 patients with mild-to-moderate AD were randomized to either EGb 761 (160 mg/day), donepezil (5 mg/day), or placebo.[99] According to Clinical Global Impression, both the Ginkgo and donepezil groups demonstrated comparable mild improvement. Both also had comparable dropout rates (20 percent for EGb 761 and 16 percent for donepezil). The investigators suggested given the comparable efficacy and safety of the two agents, GBE could reasonably be substituted for the more expensive donepezil.

GBE's efficacy and safety for AD prevention is being examined in the large GuidAge Study – a French multicenter, double-blind, randomized trial in progress.[100] A total of 2,854 subjects with memory complaints were enrolled and randomized to receive either 240 mg EGb 761 or a placebo daily for five years. Final results should be available in 2010.

Vinpocetine

Vinpocetine is an alkaloid extracted from the plant *Vinca minor* (lesser periwinkle). Vinpocetine is a vasodilator and cerebral metabolic enhancer that has shown promise for vascular cognitive impairment. In a 1989 open-label, dose-ranging trial conducted for one year with 15 Alzheimer's patients at the University of California, San Diego, doses of vinpocetine up to 60 mg/day failed to show benefit for cognition or Clinical Global Impression.[101]

Huperzine

Huperzine is an alkaloid extracted from the plant *Huperzia serrata* (Chinese club moss). In a double-blind RCT on AD conducted in China in 1995, 400 mcg oral huperzine daily for 56 days was reported to significantly improve memory, other cognition, and behavioral functions compared to placebo.[102] Yet a subsequent double-blind RCT published in 1999 by the same group reportedly found the same dose of huperzine taken for the same period failed to perform significantly better than placebo.[103] Since that time no new data from RCTs has appeared on huperzine for Alzheimer's disease. A U.S. trial is underway as of 2008.[104]

Other Botanicals

Many other botanicals have potential for AD treatment. Polyphenols have in common potent antioxidant and anti-inflammatory activity. Those currently showing the most promise for cognitive support are curcumin from turmeric, green tea catechins, blueberry flavonoids (especially the diverse assortment from lowland blueberries), and resveratrol and associated flavonoids from grapes, wine, berries, and peanuts.[105] Other phytonutrients under investigation include sage essential oil, rosmarinic acid from rosemary, and cholinergic principles from lemon balm.[106]

Amnestic Mild Cognitive Impairment (aMCI): Prodrome to AD?

Mild cognitive impairment (MCI) was first defined in 1999 as a pathological brain condition.[107] Despite its name, the degree of cognitive impairment in MCI is not so mild. The subgroup of MCI with memory impairment, termed amnestic MCI or aMCI, carries very high risk for progression to dementia.[107-110] The degree of memory impairment in aMCI marginally interferes with daily productivity and quality of life and borders on mild AD.[107,108] MCI should not be confused with age-associated memory impairment, which is an extreme of normal aging and can be annoying to the individual ("senior moments," for example), but is not a pathological condition.[111]

Among researchers in this highly active field, a consensus is emerging that aMCI represents a transitional state between non-pathological brain aging and the severe cognitive pathology of AD.[107-113] This syndrome also exhibits AD neuropathology on autopsy, and many experts believe it to be an AD prodrome.[112,113]

Diagnosing MCI

MCI is diagnosed when cognitive deterioration is not severe enough to consistently impair daily productivity, but sufficient to be annoying and noticeable by others and measurable by psychometric and other clinical assessments. By definition MCI must not be significant enough to interfere with "instrumental activities of daily living."[107] The subject will often notice functional impairments and express anxiety and/or frustration, but not be impaired to the extent the function must be discontinued. Relevant instrumental activities of daily living include the ability to hold a job, plan new enterprises, maintain hobbies or start new ones, function as a parent or grandparent, pay bills and record payments, perform home maintenance, organize and participate in social activities, and so on. If a patient has functional deficits sufficient to impair activities of daily living and the cognitive impairment affects memory and at least one other area of cognition, the diagnosis is dementia, not MCI.

Pursuant to this limited functional definition, when other cognitive functions are impaired along with memory the syndrome is MCI. When memory impairment is notably more severe than other cognitive impairments, the syndrome is specifically denoted aMCI.[107]

Noninvasive imaging technology is rapidly advancing and has improved MCI diagnosis, but psychometric and other neuropsychological testing continue to provide the most definitive and reproducible diagnoses.[107-110,114] According to Rosenberg et al, the most useful psychometric tests to detect MCI are visuoconstructional function (clock drawing test); delayed episodic verbal and logical recall (Hopkins, Wechsler); verbal category and semantic fluency (animals, words beginning with F-A-S); attention (digit span, forward and backward); processing speed (Trail Making Test Part A); and executive functioning (Trail Making Test Part B, symbol-digit substitution).[114]

A U.K. group has recommended a combination of associate learning task (PAL) and global cognition – the Addenbrooke's Cognitive Examination (ACE).[110] Computerized batteries of tests offer useful time- and cost-efficient alternative options for diagnosis.[114] For a quick and easy test the MMSE appears not to be sufficiently sensitive to reliably discriminate MCI from healthy subjects or early AD.[114] Instead, the ADAS-Cog is proving accurate and reliable; this and related tests offer potential for affordable mass screening within communities.[115,116]

Brain Imaging Helps Diagnose MCI

Although not yet sufficiently precise to reliably establish MCI or distinguish it from early AD, diagnostic brain imaging continues to make strides in this direction. PET functional imaging quantifies whole-brain or zonal glucose utilization and reliably distinguishes AD from healthy controls. A PET finding of abnormal local cerebral glucose metabolism in an MCI brain indicates a high risk of developing dementia within the subsequent two years.[36]

Single photon emission computed tomography (SPECT) imaging can detect decreased blood flow in the cortical zones. For the MCI patient, a poor perfusion pattern on SPECT similar to that seen in AD might suggest a high risk of conversion to dementia within the subsequent few years.[114]

Risk of aMCI Progression to Dementia

According to current best estimates, subjects diagnosed with MCI tend to progress to dementia, although not necessarily to Alzheimer's disease. Of those diagnosed with aMCI, at least half progress to AD. The rate of progression from aMCI to AD is in the range of 10-15 percent per year, which amounts to a possible 100 percent after 10 years.[107-110] Yet full progression is far from inevitable. In population-based studies, 20-25 percent of MCI subjects apparently revert to normal cognitive competence.[107,114]

Amnestic MCI results in AD neuropathology. Petersen et al reported that of 15 autopsied brains from aMCI individuals, all showed temporal lobe abnormalities consistent with considerable memory impairment and other pathology, on the continuum between aging and very early AD.[113] Bennett et al, examining the brains of Catholic clergy, found similar results to those from Petersen's group.[117] They also identified cerebrovascular infarctions in at least one-third of autopsied brains, reminiscent of Snowdon's assertion that significant NFTs and amyloid plaques can be present and not create AD symptoms unless circulatory damage is also present.[15]

The totality of evidence supports aMCI as a precursor of AD. However, since progression from aMCI to AD is not inevitable, it is possible early intervention at the MCI stage could slow or halt progression toward AD.

Randomized Controlled Trials in Amnestic MCI

Results of drug intervention trials for slowing the progression of aMCI have been mixed. In a double-blind RCT conducted with 1,457 aMCI subjects, the anti-inflammatory COX-2 inhibitor rofecoxib failed to slow progression to AD and possibly accelerated progression compared to placebo.[118] A recent review of eight RCTs of CI drugs for aMCI subjects (three of donepezil, three of galantamine, and two of rivastigmine) found no significant efficacy over placebo in slowing progression to AD.[119]

Another Alzheimer's Disease Cooperative Study trial compared vitamin E to donepezil for aMCI.[70] A total of 769 aMCI-confirmed subjects were randomized to donepezil, vitamin E (as DL-alpha-tocopherol, 2,000 IU), or placebo for three years; all subjects received a multi-vitamin. No significant reduction of progression occurred in either the donepezil or vitamin E group. Donepezil showed a transient and clinically marginal preventive effect after one year, with a larger and more sustained effect after two years in a subgroup of subjects who had at least one ApoE4 allele. The ADCS researchers suggested physicians recommend donepezil for aMCI on a case-by-case basis.

The results of the randomized controlled trials on aMCI to date are essentially negative.[120] The same drugs that have demonstrated limited efficacy for established AD have fared no better for aMCI.

Some physicians are embracing a more integrative approach to managing patients with cognitive impairment. For example, Rosenberg et al prescribe lifestyle changes, including moderate exercise, such as walking three times weekly, and engaging in cognitively stimulating activities that involve language and psychomotor coordination, such as crossword puzzles, dancing, and volunteer work.[114] They also recommend tight management of cardiovascular risk factors.

Given that Alzheimer's disease is virtually unmanageable, and management of its prodrome aMCI is difficult, a question arises: Is there an earlier point for intervention that might prevent AD? Components of a primary prevention strategy for AD would include, at a minimum:

- Conscientious management of modifiable risk factors
- Periodic cognitive assessments based on physician-patient vigilance
- A comprehensive total approach to personal health management

Primary Prevention of Alzheimer's Disease through Risk Factor Management

Many endogenous and exogenous AD risk factors have been documented, herein termed Alzheimer's risk factors (ARF). Other adverse factors likely contribute to AD risk but are not yet fully supported by evidence, termed Alzheimer's contributory factors (ACF). Multiple factors undoubtedly work synergistically and additively to increase AD risk.

Depending on which risk factors are involved, AD risk would not be predictable but might wax and wane as adverse factors interact. While some risk factors are not modifiable, most can be modified, especially when patients are motivated and have help from knowledgeable professionals.[121-124]

Non-modifiable ARF include age, gene mutations (early-onset AD), family history of AD, ApoE status, and Down Syndrome.[121-123,125] Modifiable ARF include hypertension, hypercholesterolemia, high homocysteine, type 2 diabetes, metabolic syndrome, obesity, heart disease, cerebrovascular disease, and folate or other B-vitamin deficiencies.

Non-modifiable Risk Factors

Age

Aging is the undisputed number one risk factor for AD. On the surface it would seem aging cannot be influenced. But with the rise of geriatric research has come the concept of successful aging.[123,126,127] In essence, successful aging ("healthy aging") implies an individual is stronger in body and mind than others of his or her age group. For an individual experiencing successful, healthy, happy aging, getting old does not mean getting Alzheimer's disease.

Drachman published an entropic ("increasing disorder") analysis of AD, accurately pointing to advancing age as the predominant risk factor for the disease and hypothesizing aging alone could account for its causation.[125] Drachman argued against seeking a single pathophysiological factor (e.g., amyloid accumulation), but rather suggested effective AD prevention might instead depend on recognition of contributions from a multiplicity of age-related changes and reducing their burden as much as possible.

Although much evidence supports Drachman's hypothesis that aging alone causes AD, one argument against it is that young people can and do get AD.[1,2] Further refutation comes from the other end of the spectrum – people are getting older without AD. Snowdon continues to track the School Sisters of Notre Dame.[15,128] Most of the nuns over age 100 did not have AD or any progressive cognitive pathology. Similarly, among hundreds of over-90 cognitively healthy elderly seen in his clinic (as prospective organ donors), Sabbagh found 90 percent showed no Alzheimer's brain changes on autopsy.[122]

Elegant, cutting-edge research from Black et al[126] also argues against the entropic aging hypothesis of Drachman, instead suggesting the brain have powerful adaptability (often called neuroplasticity or plasticity[129,130]). Using rodents, the cage environment was manipulated to provide varying degrees of stimulation. The more opportunities the animals had to exercise their brains (e.g., colored toys) and bodies (treadmills, usually), the more plasticity emerged, including new brain synaptic connections, dendritic branches, capillaries, and non-neural support tissue. Black's group interprets their findings in favor of the "use it or lose it" hypothesis, which originated from Swaab.[127]

The robust brain plasticity of laboratory rodents arguably also exists in humans. New techniques for noninvasive imaging of the living brain have discovered the visual cortex of mice and primates (macaques) creates about seven percent new synapses per week.[129] In a stimulating book, *The Brain that Changes Itself*, Doidge gives many examples of brains severely abnormal from birth or seriously injured in adult life that were markedly restored.[130]

Genetic Susceptibility

Although late-onset AD, the most common form of the disease, has relatively minor heritability,[1] the apolipoprotein E4 gene allele is a major risk factor for early- and late-onset AD. Even though a double dose of ApoE4 alleles greatly increases the risk, ApoE4/4 homozygotes do not inevitably get AD. Early-onset AD has much greater heritability, which is thought to be the cause of its accelerated emergence. Although no expert consensus exists, for individuals who experience AD onset before age 60 heritability appears to be about 50 percent.[131,132] After age 60, genetic risk factors may be relatively negligible compared to environmental risk factors.[133]

All too often in discussions of the heritability of disease, genetic determinism comes to the forefront, and so it is with Alzheimer's disease. While it is possible (and reasonable) for some experts to use sibling and twin studies to conclude AD has high heritability (e.g., greater than 50-percent[131]), the findings that certain U.S. populations have significantly greater risk for AD than related populations in other countries support an environmental etiology. Thus, Grant has pointed out African Americans have four times the risk of AD

compared to native Nigerians, and Japanese-American men in Hawaii have 2.5 times the risk of native Japanese men.[132] He suggests the high total calorie and fat intakes in the United States are responsible. Considering the known modifiable AD risk factors, concerned individuals and healthcare providers have the tools necessary to develop an AD prevention program.

Down Syndrome

Down Syndrome (DS) is firmly established as highly heritable and a major risk factor for AD (emerging most often during the fourth decade of life in virtually 100 percent of DS subjects).[134] DS is a developmental disorder caused by inheritance of an extra copy of chromosome 21, although the etiological relationship between the chromosome 21 genes and the DS phenotype is complicated.[134] Excessive amyloid production in the brain has been reported from cases as young as 14, and hippocampal dysfunction as judged from neuropsychological tests has been recorded as early as age 11.[135]

A gene that encodes for amyloid precursor protein (APP) resides on chromosome 21.[136] It is thought in DS the extra copy of the APP gene once activated can cause abnormalities in the processing of amyloid and its subsequent deposition in plaque. Other than in DS, inherited alteration of this gene causes an autosomal dominant form of AD.[136]

Prior Traumatic Brain Injury (TBI)

All major head injuries, including concussions, can significantly increase the risk of AD.[137-139] Within a few hours following TBI, abnormal patterns of amyloid and tau deposition appear in injured brain tissue.[138] Repeated mild TBI accelerates amyloid deposition and speeds cognitive impairment.

TBI can result in a two- to four-fold increase in AD risk, and indications are the more severe and repeated the TBI, the greater the cumulative risk for AD later in life. Sports such as boxing, ice hockey, soccer, and football facilitate head impacts. Boxers who have had 10 or more brain injuries and who have the ApoE4 gene tend to have worse cognitive outcomes than those lacking the gene.[138,139] The putative relationship between TBI at any stage of life and elevated risk for AD in later life should be a priority for future investigation.

Modifiable Risk Factors

Smoking

Anstey et al conducted a meta-analysis of the association between smoking and dementia/cognitive decline.[140] From data on more than 43,000 individuals followed for 2-30 years, they found smokers had almost twice the risk for an AD diagnosis. Sabbagh et al examined the relationships between smoking, AD, and lifespan.[141] They concluded that individuals who were smokers at the time of AD onset tended to die from the disease eight years earlier than nonsmokers. They also reported a dose-dependent effect on disease duration – the greater the pack-years, the sooner the patient died of AD.[141]

Hypertension, Other Cardiovascular Abnormalities

Hypertension, elevated cholesterol, and atherosclerosis are established risk factors for AD,[142-144] hypertension in particular.

Although poor brain circulation has been more closely linked to vascular dementia than to AD, many cases of AD are complicated by the presence of micro-lesions denoting blood vessel breakages – mini-strokes.[143,144] These are often clinically silent, escaping detection but exacerbating AD progression. In the Nun Study, Snowdon observed the majority of those with clinical AD at death had tissue scarring from mini-strokes in addition to amyloid plaques and NFTs.[15,144]

Hypertension at midlife is linked to significantly increased risk for AD.[142] A program to detect and manage hypertension could remove a modifiable risk factor while also lowering the risk for stroke or other cardiovascular event.

Homocysteine

An elevated blood level of homocysteine, a metabolite of methionine, is a risk factor for AD.[145] By following 1,092 subjects for eight years, the Framingham Study found high plasma HCy (greater than 14 mM/L) doubled the risk for AD.[146] In 2003, Miller comprehensively reviewed the studies that linked HCy to increased AD risk,[83] documenting many studies indicating vitamins B_6, B_{12}, and folate can effectively lower homocysteine.

The magnitude of the association between HCy and AD may increase with age[146] and appears to plateau around age 60. This makes management of homocysteine in midlife perhaps comparable in importance to cholesterol management.

Obesity

Obesity is a proven risk factor for AD. A Finnish study that tracked 1,500 people for 18 years concluded midlife obesity more than doubles the risk for AD.[147] Obesity with hypertension and high cholesterol elevates the risk six-fold. Another population-based study, which followed more than 10,000 people for over 27 years, reported obesity increased AD risk by 75 percent. This study also suggested that waist fat ("central obesity") increased AD risk, regardless of whether the individual was obese, overweight, or within the normal weight range with abnormal fat distribution.[148]

Type 2 Diabetes/Insulin Resistance

Type 2 diabetes is linked to higher AD risk.[1,149-151] In diabetes, hyperinsulinemia almost doubles the risk for AD compared to people without diabetes.[149,150] There is also good evidence hyperinsulinemia accelerates functional cognitive decline.[151] Furthermore, insulin resistance is implicated in the pathogenesis of AD.[150] Elevated glycosylated hemoglobin (HbA1C) over 15, a test for long-term blood sugar control, increases AD risk.[149]

Likely Alzheimer's Contributory Factors (ACF)

The brain inherently carries a high metabolic and free radical burden and functions in delicate balance between health and ill-health.[152] As a consequence, virtually any factor adverse to the health of the body as a whole is adverse to brain health. Several known factors that lack full documentation for being ARF, but likely to contribute to AD risk, are discussed in the following sections.

Mercury and Other Metals

Many metals are toxic to living systems.[153] Mercury is the most toxic heavy metal for the brain. A comprehensive search of the literature does not disclose a consistent correlation between mercury in amalgams or body mercury burden and risk for AD. Despite many studies, mercury from dental amalgams has not emerged as an ACF.

But this issue cannot yet be dismissed. A 2002 study in Scotland compared 180 practicing dentists to 180 control subjects for mercury status, cognition, and behavior.[154] The dentists had urine mercury levels four times higher than controls and demonstrated significantly higher frequency of kidney disorders and memory disturbances. Many national and provincial regulatory authorities, including in the United States, have enacted stringent occupational procedures to protect dentists from exposure to mercury-containing dental amalgams. If dentists are considered to be at risk from dental amalgam exposure, it seems logical that patients are potentially at risk as well.

While this controversy continues, a seemingly obvious question apparently has not been addressed in the peer-reviewed literature: Could mercury at lower body burdens than those currently recognized as toxic operate additively or synergistically with other heavy metals or environmental toxins to increase oxidative stress in the brain? An informed observer might also question whether mercury reaching the brain from amalgam or other sources, such as contaminated foods, might interact negatively with redox-active transition metals intrinsic to the brain, such as iron or copper.

Aluminum (Al) is a neurotoxin so abundant in soil it cannot be avoided in the food supply. Drinking water, weakly associated with AD risk, supplies only one-ninth of the total daily Al intake compared to foods.[155] Massive Al exposure from kidney dialysis can cause dementia, although not identical to AD.[155] Al requires further investigation as an Alzheimer's contributory factor.

C-Reactive Protein

C-reactive protein (CRP) is a biomarker for systemic inflammation and a confirmed risk factor for cardiovascular disease.[156] A 2005 examination of CRP and cognitive performance identified six studies, all of which reported some positive association between elevated CRP and cognitive decline or dementia risk.[156] One prospective study, the Honolulu-Asia Aging Study, followed 1,050 Japanese men for up to 25 years, beginning at average age 55.[157] Men in the upper three quartiles

of CRP concentration had significantly increased risk for AD compared to those in the lowest quartile. These findings, although preliminary, are consistent with neuropathological evidence strongly suggesting inflammation contributes to AD.[1,2,8,10]

Hypothyroidism

In 1991, Breteler et al reanalyzed eight case-control studies on thyroid function and AD and found the rate of hypothyroidism was increased in AD cases compared to controls (relative risk 2.3; 95% confidence interval 1.0-5.4).[158]

In a 2006 longitudinal study, 1,077 elderly subjects (ages 60-90) free of dementia at baseline were followed for a mean 5.5 years.[159] Serum TSH and thyroid hormones (nonfasting) were found to be unrelated to AD risk. One finding, however, was that nondemented subjects with higher T_4- and T_3-receptor levels had more hippocampal and amygdalar atrophy on MRI imaging. Labudova et al found the receptor for TSH is over-expressed in the AD brain.[160] The possibility that some feature of thyroid status contributes to AD risk awaits further investigation.

Epilepsy

The aforementioned 1991 Breteler reanalysis of eight case-control studies also examined epilepsy.[158] The researchers found more AD cases than controls reported epilepsy before onset of AD (relative risk 1.6; 95% confidence interval 0.7-3.5), especially for epilepsy onset within 10 years of onset of dementia.

Electromagnetic Fields (EMF)

The potential negative health effects of EMF have increasing relevance considering their ubiquitous nature. A 2007 case-control study at the University of Southern California looked at 1,527 cases of probable or definite AD and compared EMF occupational exposures to those of 404 controls with cognitive dysfunctions.[161] The three occupations with the highest EMF exposures were pilot, sewing machine operator/clothing cutter/dressmaker, and welder. Calculated two ways via methodological refinement, the odds ratios for increased AD risk were 2.2 ($p < 0.02$) and 1.9 ($p < 0.03$). This suggests that subjects with the highest EMF exposures had 2.2 or 1.9 times greater risk of developing AD compared to individuals with the lowest exposures.

Preventive AD Factors

Physical Exercise

Physical activity enhances cognitive and brain function.[162] The hippocampus and cortex generate nerve cell precursors from stem cells throughout life.[163] In animal experiments, physical exercise increases mitosis in this zone, leading to new nerve cells.[162] Conversely, lack of exercise inhibits the differentiation of newly generated precursor cells into functional brain cells.[163]

The findings from animal research have spurred human studies.[163-166] A majority of the epidemiological, population-based studies found individuals who exercise more than three times weekly have significantly lower dementia risk than those who exercise less.[164-167]

Findings from controlled clinical trials support a positive correlation between physical exercise and cognition. Meta-analyses confirm normal and cognitively impaired adults derive benefits from physical exercise that seem to be greatest for executive control processes (e.g., planning, scheduling, working memory, dealing with distraction, multitasking).[165,166] This is an important finding given these processes tend to substantially decline with advancing age.[166,167]

Relatively few studies have correlated physical exercise with changes in human brain structure and function. Walking (more than one hour daily, three days a week) can increase gray matter volume in the frontal and temporal cortex, whereas non-aerobic exercise apparently does not.[165] Research with rodents established that aerobic exercise elevates growth factors and other neurogenesis (stem cell differentiation and new circuit formation) promoters in the cortex, induces new capillary development, and increases cell proliferation and cell survival.[163,167] Although neurogenesis normally decreases with age,[163,167] in rats exercise reverses this decline even as it improves cognitive performance.[162,167]

Physical exercise undoubtedly has pleiotropic health benefits. By increasing blood flow (and probably via other less well-understood mechanisms) it reduces risk for heart attack, stroke, and diabetes, all linked to accelerated cognitive decline.[164-166,168]

Mental Exercise: Training the Brain

As with physical exercise, animal experiments demonstrate mental exercise supports neurogenesis, while lack of mental exercise and stress allow stem cell progeny to die off.[154] According to the paradigm of brain plasticity, it should be possible to remold and even rebuild the brain through "brain training" – an interesting area of brain health management. Also called neurobics or brain fitness, this activity involves mental exercise using video games, DVDs, online courses, interactive tests, or other media; and some are proving effective.

A 2006 article in the *Journal of the American Medical Association* reported on a single-blind RCT that divided 2,832 elderly volunteer subjects (mean age 73.6) into four groups (memory, reasoning, processing speed, and controls) for cognitive training.[169] Each group received 10 weeks of training, then a four-session "booster" 11 and 35 months after training. At a five-year follow-up the three actively trained groups demonstrated significant cognitive improvement over the controls.

Outcomes from brain training suggest the human brain is resilient and are consistent with animal findings[126,127] and clinical observations[130] that the brain is capable of rebuilding lost circuits.

Age-Associated Memory Impairment (AAMI) for Early Intervention

Defining and Diagnosing AAMI

Given that AD and aMCI represent severe pathologies, even when first diagnosed, it is desirable to diagnose cognitive impairment at an earlier stage. Healthy people experience noticeable loss of memory and other cognitive abilities as they age. However, some individuals experience cognitive decline that measurably exceeds their peers, although not severe enough to be diagnosed as aMCI or AD, and can be diagnosed with AAMI.

AAMI was identified in 1986 after the U.S. National Institute of Mental Health convened a panel of brain-aging experts to develop operational criteria for this condition.[111] The panel defined AAMI as a nonpathological condition akin to the fading of eyesight with age. They developed inclusion criteria for AAMI: (a) over age 50, (b) not demented, (c) intellectual function adequate to remain productive, (d) complaint of gradual memory loss since early adulthood, and (e) objective evidence of memory loss on performance tests. Exclusion criteria for AAMI include severe memory loss approximating AD, other known dementia, or other medical or psychiatric condition that could produce memory loss.

AAMI is also recognized by the American Psychiatric Association.[5] The American Psychological Association uses the term "age-consistent memory decline."[170] Subjects over age 50 are subjected to standardized memory tests and scores are compared to mid-20 adults. Those who score in the bottom one-third of this distribution are classified AAMI. The lowest scoring AAMI individuals are candidates for further testing to probe for aMCI.

To establish normal ranges of memory function at younger ages, Crook et al studied tens of thousands of individuals from different cultures and obtained similar psychometric data for decade-by-decade cognitive declines in subjects from Belgium, Italy, San Marino, the United States, and Sumatra.[171,172] Using these strong baseline validations, Crook's team subsequently established that 40 percent of people ages 50-59, greater than 50 percent of individuals ages 60-69, and up to 80 percent of those over 80 can receive an AAMI diagnosis.[172] There is disagreement in the literature whether AAMI carries a heightened risk for AD; Crook states there is no additional risk,[173] while Goldman and Morris assert a three-fold increased risk for progression to AD.[174] These differences may be related to the two groups using different types of tests to diagnose AAMI. Whether progression occurs, individuals with AAMI can experience depression, fear of AD, and significantly diminished quality of life.

Clinical Trials of AAMI

Relatively few peer-reviewed journals have published AAMI trials. The plethora of terms associated with the concept – age-consistent memory decline, age-related cognitive decline, age-associated cognitive decline, benign senescent forgetfulness – can all be confused with AAMI and make search for studies difficult.

Crook et al conducted a double-blind RCT of phosphatidylserine for AAMI.[175] The trial emphasized

both clinical assessment and psychometric testing validated to real-life situations. After three weeks, the PS group (300 mg/day) demonstrated significant improvement over the placebo group on memory tests, including remembering names and faces, telephone number recall, and placement of keys and glasses. After three months, PS improved memory by 30 percent compared to placebo. A subgroup who scored poorest entering the trial showed the most benefit; researchers calculated that, for name and face recall, PS had "rolled back the clock" by roughly 12 years. At baseline, individuals in this subgroup scored a "cognitive age" of 64. After three months on PS, however, these individuals demonstrated an average cognitive age of 52.[175]

In 2005, Crook's team published a one-month, double-blind RCT on AAMI with a proprietary nutrient mixture consisting of several neuropeptides (short chains of amino acids; N-PEP-12). The researchers reported N-PEP-12 improved memory and several other cognitive measures.[176]

Ginkgo (EGb 761) was tested for AAMI in a double-blind RCT. In two publications the researchers reported finding no benefit from EGb 761, even at 240 mg/day for six months.[177,178] The trial included subjects with AAMI or dementia, which may have decreased its statistical power. The psychometric data approached statistical significance, attaining 90-percent confidence in favor of Ginkgo over placebo.

Citicoline was tested in a double-blind RCT with an aging population who demonstrated average test scores for the age group (total 95 subjects, average age 67 years).[179] The subjects received citicoline 1,000 mg/day or a placebo for three months. Then a subgroup was identified, with poorer-than-average memory, to participate in a crossover trial of 2,000-mg citicoline daily or placebo for an additional two months. This relatively poorly performing subgroup (n=32, averaging 6-8 years older than the total sample), which may have included some who fit the criteria for AAMI, demonstrated improved verbal memory in the citicoline group.

In view of the fact that early intervention may be the key to halting progression to aMCI or AD, more trials are warranted.

Conclusion

AD is a devastating disease that is in its infancy in regard to understanding its pathology and potential treatments. The approved cholinesterase inhibitor and NMDA-receptor blocking pharmaceuticals have not been effective.[39] Other pharmaceutical classes such as statins[180] and COX-2 inhibitors[118] have shown no efficacy in randomized controlled trials.

A vaccine trial using anti-amyloid antibodies failed to demonstrate efficacy, with 18 of 360 subjects suffering serious adverse effects.[181] A human gene transfer experiment, injecting cells into AD brains, demonstrated that raising nerve growth factor levels in the forebrain slowed AD progression, although two of eight patients were brain-injured during the injection procedure and one died.[182]

Omental transposition surgery involves transposing a flap of intestinal omentum over the brain surface. Omental tissue is rich in growth factors, some of which enter the brain. Although this procedure has seemingly helped some AD patients, it is relatively complicated and expensive.[183] Given the lack of medical management options for AD, primary prevention and early intervention may be the best approaches.

Elements of Primary AD Prevention

The yearly U. S. cost estimate for AD is $300 billion. Primary prevention of AD could begin with mass education about brain health, taking advantage of the electronic age. Brain training as well as mass screening of cognitive performance is feasible using psychometrics. Other cost-effective elements of an integrative primary prevention program could be provided for at-risk populations, perhaps online.

Snowdon's study population,[15] the Catholic order School Sisters of Notre Dame, is a model for preventing AD through comprehensive health management. Some experts contend everyone will get AD if they live long enough, but for at least the first century of life the Nun Study suggests AD is not inevitable since most who surpassed age 100 demonstrated no functional AD symptoms or hallmark signs of amyloid or NFT on autopsy. The nuns live a low-stress, satisfying life, consume a healthy diet high in fruits and vegetables, and engage in regular yoga and aerobic exercise, suggesting late-onset AD may be primarily a result of lifestyle.

Although stress is not a proven contributing factor to AD, stress reduction should be part of a comprehensive AD prevention program. Stress can damage or destroy nerve cells in the brain, with particularly deleterious effects on the hippocampus, the primary area that initiates memory of new experiences.[184,185] A long-term clinical study at Canada's McGill University recruited middle-aged volunteers, determined hippocampal volumes using MRI, then tracked them for five years.[186] The sample included "good stress copers" and "bad stress copers." Those who coped badly with stress manifested hippocampal atrophy and scored significantly lower on memory tests than did the good stress copers. These findings correlate with animal experiments that find chronic stress causes brain neuron death and hippocampal atrophy.[184] Meditation can mediate stress by decreasing blood cortisol levels, increasing the calming hormones melatonin and serotonin,[187] improve sleep quality, and increase pain tolerance.

The human mind and body has finite limits in coping with stress, whether metabolic, chemical, electromagnetic, or emotional in origin. The brain is delicate and vulnerable to insult. Lifestyle factors that can be modified to decrease risk include diet, intervention with specific nutrients, exercise (both aerobic and mental), stress reduction, weight loss, and smoking cessation.

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