Stopping the clock:
Therapeutic interventions in Alzheimer's disease

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The ticking clock

The memory impairment of Alzheimer's disease is thought to be the end result of a complex interplay of aetiological factors that lead to the neurotransmitter failure discussed in *'The ticking clock'*, part 1 of this 2 part overview of therapeutic interventions in Alzheimer's disease.[1] Current research focuses on an understanding of these aetiological factors and on the development of interventions that may stop or reverse the sequence of events leading to cerebral neurotransmitter failure, giving hope for the restoration of cerebral function or, in the metaphor of Milton's *Paradise Regained*, hope of *'Eden raised in the waste wilderness'*.[2] The impact of Alzheimer's disease on the community as well as on the individual increases with time. In our community, the structure of our population is changing with rapidly increasing numbers in the older age group and it is in this very group that there is an increasing incidence of 'brain failure'.

The impact

The unprecedented 'graying' of the population causes concern regarding the burden of chronic diseases, including Alzheimer's disease (AD), throughout the world. By 2051, 25% of New Zealanders will be over the age of 65 years compared with 12% in 2001, the greatest increase being among the very old. In 2051, for every person over the age of 65 years there will be 2.3 people in the working age group compared with 5.5 people in 2001 – an increased dependency ratio.[3]

The prevalence of dementia increases by about 1% per annum in people over the age of 65 years and affects up to 30% of those over 85 years of age. There are approximately 38 000 people in New Zealand suffering from dementia now and, in the years to come, the numbers of those suffering from dementia will increase rapidly as the proportion of the very old in the population increases, challenging the ability of the community to meet their needs. At least 50% of those with mild dementia live in their own homes with the support of family members and community services including day care and respite care. The stress of caregiving in this situation can lead to the breakdown of support and precipitate admission into residential care where 60–70% of residents suffer from some form of dementia.[4]

The cost of medical and nursing care for patients with AD in the US is estimated at $27,000 per annum, placing it among the most costly of illnesses. Cost of care increases with the severity of disease. The burden of care is great as 80% of caregivers report stress and 50% report depression.[5] Any interventions that can prevent this disease or slow or halt its progress will have major cost benefit implications for the community and quality of life implications for patients and caregivers.

The cause

Oxidative stress

Oxidative stress may well cause the DNA damage that triggers AD and may be the primary aetiological factor in its pathogenesis. Changes related to oxidative stress have been demonstrated in the brain and peripheral tissues of patients with AD and the relatives of those with familial AD.[6]

Genetic factors

Genetic factors at multiple loci have been shown to influence the accumulation of amyloid beta-peptide and the development of AD, different groups of genes affecting the age of onset of the disease. For early onset AD, mutations in three genes (amyloid pre-

cursor protein [APP], presenilin 1 [PS1], and presenilin 2 [PS2]) cause autosomal dominant, early-onset familial AD but together account for <2% of all cases. A fourth gene, apolipoprotein E (APOE), increases risk of the more common late-onset familial and sporadic forms of AD. The APOE-4 allele increases risk and reduces age at onset of AD in a dose-dependent manner. Mutations on other chromosomes have been linked to familial AD and are associated with different ages of onset.[7]

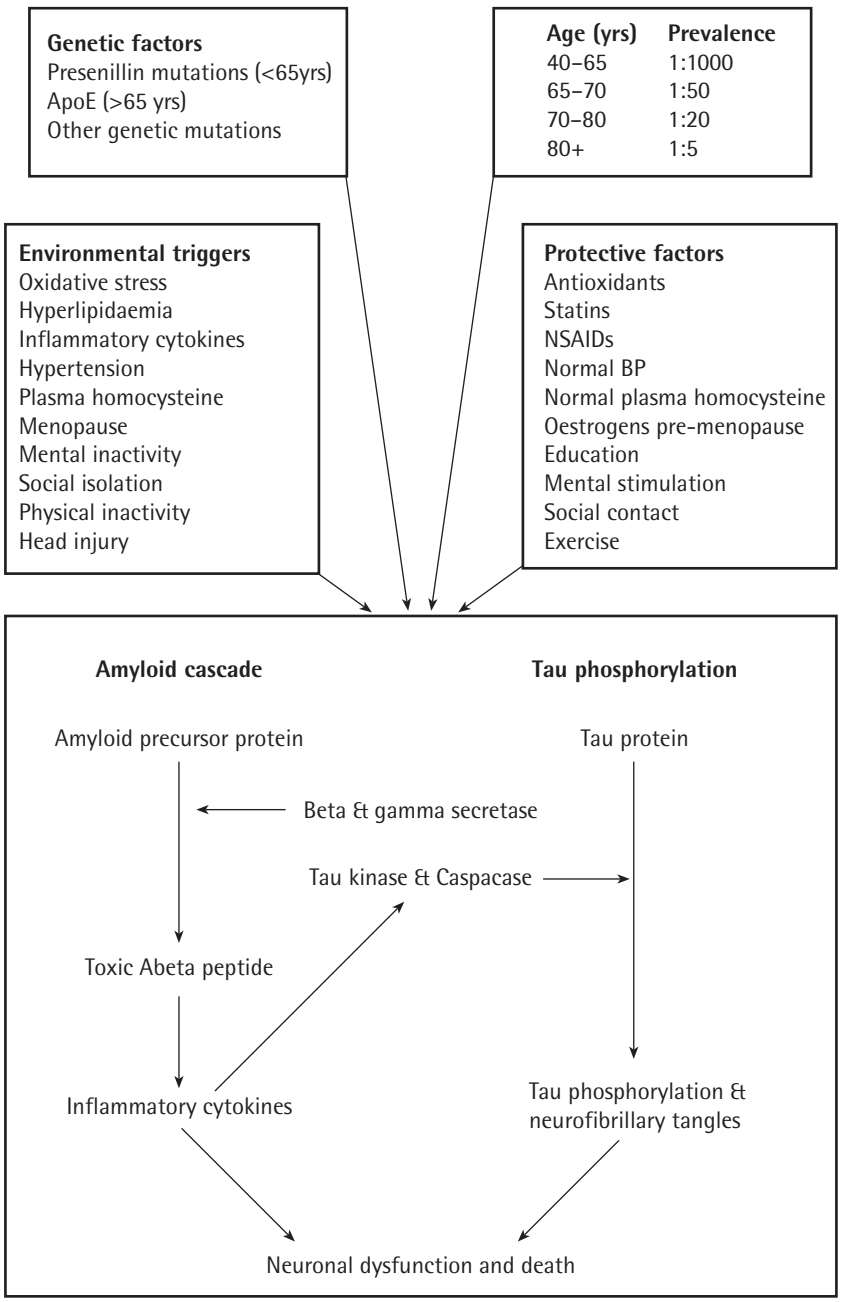
The amyloid cascade

The hallmarks of AD pathology are the presence in the brain of amyloid plaques, intracellular neurofibrillary tangles which consist of phosphorylated tau protein and progressive loss of brain substance. Genetic, biochemical and pathological evidence suggest that abnormal processing of amyloid precursor protein leads to the accumulation of toxic amyloid beta-peptide (Abeta) in the brain and cerebral blood vessels.[8,9] Cleavage of amyloid precursor protein by alpha secretase produces a non-toxic end product whereas cleavage by beta secretase and subsequently gamma secretase results in the production of toxic Abeta peptide.[9] According to the amyloid cascade hypothesis, the neuro-degenerative process in AD is triggered by oxidative stress[10] and inflammatory cytokines produced by Abeta. Abeta accumulates as amyloid plaques in the brain and also activates kinases that trigger the deposition of phosphorylated tau protein as neurofibrillary tangles. These changes lead to cellular dysfunction and subsequently death, failure of neurotransmission and the clinical presentation of dementia.[8,9]

Tau Phosphorylation

Tau protein is involved with cellular transport systems and undergoes phosphorylation in the normal course of its function. It is thought that high phosphorylation of tau protein and cleavage of tau protein with the loss of segments of the molecule causes loss of function. The abnormal tau proteins stick together forming neurofibrillary tangles. Loss of function of the abnormal tau protein and the formation of neurofibrillary tangles contribute to loss of neuronal function and cellular death.[11]

Figure 1. Alzheimer's disease: evolution



Alzheimer's disease and vascular dementia

Current theories suggest that the distinction between AD and vascular dementia is less clear cut than was previously thought. Cerebrovascular disease and AD co-exist and cerebrovascular dysregulation, which is an important feature of AD, may contribute to impaired clearance of Abeta across the blood brain barrier with resultant neurovascular inflammation, cerebral hypo-perfusion, neurodegeneration and cognitive decline.[12] Clinical dementia is often associated with the co-existence of AD and cerebrovascular pathology

and the control of cardiovascular risk factors, in particular hypertension and hyperlipidaemia, and measures to prevent recurrent strokes are important strategies for slowing the progression of dementia.[13]

Cholesterol metabolism

Abnormalities in lipid metabolism occur in the ageing of normal brains and also in the brains of patients suffering from AD. Lipid accumulation may be found early in the course of the disease in vulnerable areas such as the Hippocampus and may increase the production of Abeta by enhancing gamma secretase cleavage of amyloid precursor protein. Studies suggest that the toxic effect of Abeta, with resultant oxidative stress, triggers membrane lipid abnormalities in AD, thus producing a vicious cycle for the production of neurotoxic agents. The lipid alterations themselves may cause neuronal synaptic dysfunction, neuronal degeneration and death.[14]

Stopping the clock

Years before dementia becomes apparent, physical and environmental triggers may pave the way for the development of AD. While no proven disease modifying interventions exist at present, the focus of current research is on the identification of factors that may prevent or interrupt the amyloid cascade and on the development of drugs that may stop or reverse these pathological changes.

Genetic manipulation

Studies involving transgenic mice have shown that AD, produced in these animals, can be halted or even reversed by genetic manipulation.[15] We are a long way from applying this to humans.

The amyloid cascade

Antioxidants target the amyloid cascade at the level of oxidative stress. Vitamin E and selegiline could both be considered 'probably beneficial'.[9] Although the Cochrane database finds insufficient evidence to recommend the use of Vitamin E for therapy in AD, justification for further studies is found.[16] A recent meta-analysis of high dose vitamin E supplementation suggested a possible increase in all cause mortality associated with doses above 400IU bd. These results should be interpreted with caution because of the small numbers of subjects involved.[17] Vitamin E in food, as opposed to supplements, has been shown to protect against the development of dementia.[18] The effectiveness of Gingko Biloba remains controversial. A trial of Gingko Biloba in older people without dementia is underway. Modest benefits have been observed in some studies for patients with both AD and vascular dementia using doses of 120–240 mg per day and it can also be classified as 'probably beneficial'. Trials of other antioxidants (Vitamin C and Selenium) and of antioxidant 'cocktails' have been proposed.[9]

Reduction of amyloid deposition

Abeta immunisation has been trialed in an effort to reduce Abeta burden. While this strategy was successful in clinical trials in mice, trials in humans were halted in 2002 when 6% of the subjects developed meningoencencephalitis.[8] Alternative methods of immunisation are being explored.

Inhibition of beta or gamma secretase: drugs that aim to reduce Abeta production by inhibition of these enzymes are being developed.

Inhibition of tau phosphorylation by kinase inhibition has been considered. Lithium and Valproate which have complex neuroprotective effects, including inhibition of tau kinase, are currently under investigation.[9]

Anti-inflammatory medications: Epidemiological studies suggest that use early in life may protect against the development of AD – but therapeutic trials in established disease have failed to show any effect.[9]

Oestrogens may have cholinergic, neurotrophic and neuroprotective effects and may enhance cognitive function. However, clinical trials of oestrogen showed worsening in cognition and safety problems including deep venous thrombosis in 5% of subjects.[9] The Womens Health Initiative Study indicates an increase in the risk of probable dementia associated with use of HRT in women aged 65 years and over.[19] In a recent study, Raloxifene, a selective oestrogen receptor modulator,[20] at a dose of 120mg per day, reduced the incidence of mild cognitive impairment in postmenopausal women by 33%.[21]

Statin therapy has been shown, in cross-sectional epidemiological studies, to be associated with a decreased prevalence of AD.[9] No therapeutic benefit in patients with AD has been demonstrated to date and a word of warning has been issued with regard to possible adverse effects of statins on cognition in patients with AD. It is suggested that there is a need for trials comparing the effect of hydrophilic and lipophilic statins on cognition in AD, as these drugs are not therapeutically interchangeable, and that hydrophilic statins (e.g. pravastatin or fluvastatin), which do not cross the blood/brain barrier, might be less likely to produce adverse effects than lipophilic statins (e.g. simvastatin, lovastatin and atorvastatin).[22]

Risk factors for vascular disease

Because of the role played by vascular disease in the aetiology of AD it is logical to assume that targeting vascular risk factors would reduce its incidence. Raised systolic blood pressure and raised serum cholesterol in mid life are associated with the development of AD in later life.[23] Control of hypertension (with avoidance of hypotension, as poor autoregulation in vascular dementia increases its deleterious effects on cerebral blood flow) is advised as well as dealing with other risk factors such as hyperlipidaemia, diabetes, cigarette smoking, excessive alcohol consumption, obesity and lack of exercise.[24] One study has shown a 65%

increased risk of developing AD in diabetics when compared with non-diabetics,[25] and research is underway to assess the effectiveness of optimal diabetic control in its prevention. Elevated plasma homocysteine is an independent risk factor for Alzheimer's disease and a trial of folate in combination with B6 and B12 has been undertaken.[9]

Lifestyle factors

While it is not possible to halt the march of time or, at present, to change genetic makeup, lifestyle factors can be changed for the better. Studies have shown that both mental and physical activity reduce the risk of developing AD. Higher levels of education in early life, ongoing participation in mentally stimulating and challenging educational activities and leisure pursuits and social interaction – an enriched environment – have been shown to protect against cognitive decline even in the presence of the pathological changes characteristic of AD.[26–29] Physical activity contributes not only to cardiovascular fitness but also improves cerebral function and reduces the cerebral cortical loss that occurs with ageing.[30–33]

Dietary factors

The incidence of AD was reduced in a study population that ate fish at least once a week and this was also related to the total consumption of omega-3 fatty acids.[34] Dietary niacin has also been shown to protect against AD and cognitive decline.[35]

Figure 2. Alzheimer's disease – stages and diagnosis[37,38]

Presymptomatic stage – e.g. genetic mutation carrier

Mild cognitive impairment – Progress to AD at 8–15% per annum

Alzheimer's disease

	Mild	Moderate	Severe
MMSE	21–26	10–20	<10

Onset between 40 and 90 years (early onset below 65 years).

DSM IV criteria for diagnosis of AD:

Gradually progressive memory loss plus at least one of the following:

Aphasia	Impaired abstract thinking
Apraxia	Impaired judgment
Agnosia	Personality change

Significant social or occupational impairment,
Not solely associated with an episode of delirium
Not accounted for by a non-organic mental disorder
Not accounted for by other organic causes of cognitive decline

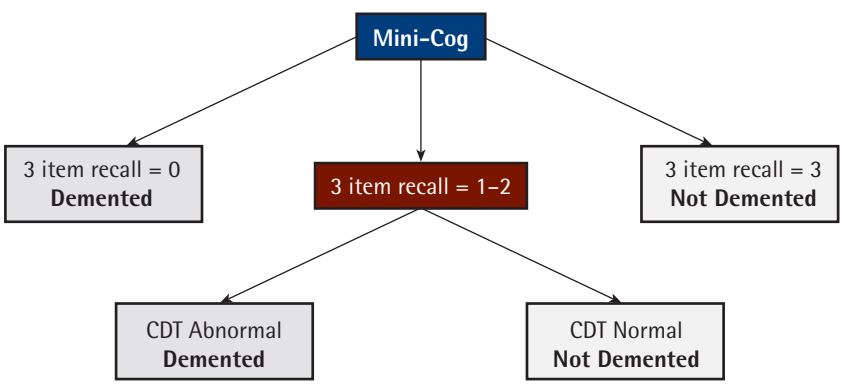
Early diagnosis

The diagnosis of AD depends on the history of gradual and progressive memory loss associated with losses in other cognitive domains. The history should be confirmed from sources other than the patient and other diseases and conditions causing cognitive decline should be excluded on the history, by physical examination and from the results of investigations.

Mild Cognitive Impairment (MCI) represents a transition stage between normal ageing and AD. Patients presenting with MCI – usually with memory impairment but continuing to function normally in activities of daily living and with none of the other criteria necessary for the diagnosis of AD – convert to AD at a rate of up to 15% per annum. Some people with MCI, however, remain stable and others may recover. The ability to identify those who will develop AD would enable the introduction of appropriate therapy before cerebral function is irretrievably compromised. Genetic testing can identify carriers of genes that increase the risk of developing AD but do not identify those that will progress to dementia. Blood levels of Abeta protein do not correlate with the degree of plaque deposition in the brain but refinements of this test may provide a suitable diagnostic test. A recent study suggests that magnetic resonance spectroscopy of the occipital cortex can identify those likely to convert from MCI to AD within the next three years.[36] Refinements of this test may offer early diagnostic confirmation of AD.

The 30 question Mini Mental Status Examination,[39] which assesses orientation, attention, recall, language and ability to follow commands, is useful for assessing cognitive function and for monitoring change over time, but performance

Figure 3. Mini-Cog scoring algorithm[45]



is influenced by the patient's age and education.[40,41] Judgment and insight are not tested and additional questions to explore these areas are often added. The 10 question Mental Status Questionnaire is a briefer screening test and has been commonly used.[42] Without formal testing, early cognitive decline can be difficult to detect in the time frame of a consultation. It is important for general practitioners to be watchful for signs of deterioration in activities of daily living (ADL) function and cognitive deterioration.[41] as there is evidence the dementia is undetected in 40% – 75% of cases in primary care.[43] While GPs believe that screening for dementia in the elderly is worthwhile, a recent survey suggests that only 24% routinely screen their own patients for dementia, the reasons given being lack of time, fear of offending patients and the inadequacy of available tests. When a screening test was used, the MMSE was usually chosen.[44] A briefer test than the MMSE for use in the surgery would be of value for initial screening of elderly patients and such a test is the Mini-Cog which takes three minutes to perform and is a composite of a three-item recall and clock drawing test (CDT).[45] The Mini-Cog attained 99% sensitivity and 93% specificity in a population containing 50% of patients with dementia, can be used by untrained persons, is not influenced by education and performs well in patients with a poor command of English.[43,44] For the three item recall, one point is given for each of the three unrelated words (e.g. shoe, flag, tree) correctly recalled as in the MMSE. For the clock drawing test, the subject is asked to draw a clock, fill in the numbers on the clock face and set the hands at 8.20. The clock is graded as normal if all numbers are in the correct sequence and position and the hands readably display the requested time. The subject is asked to repeat the three words, draw the clock, which is scored as normal or abnormal and which also serves as a recall distracter, then recall the three previously presented items. Subjects recalling none of the words are classified as demented, those recalling all of the words are classified as non-demented and those with intermediate word recall (one to two) are classified based on the CDT – (abnormal=demented, normal=non-demented).[45]

General practitioners will have a key role to play in early diagnosis so that therapy can be commenced before irreversible cognitive decline occurs

Summary

Addressing lifestyle and dietary factors may offer some protection from AD. Current research seeks to identify interventions that may prevent the transformation of MCI to AD or halt its progress and, as these become available, the focus will shift from the diagnosis of delirium and exclusion of reversible cause of dementia to the early diagnosis of dementia. General practitioners will have a key role to play in early diagnosis so that therapy can be commenced before irreversible cognitive decline occurs.

Key Points

- Prevention – now:
  - Physical exercise
  - Mental exercise
- Diet:
  - Fish: Omega 3 fatty acids
  - Niacin
  - Vitamin E
- Control cardiovascular risk factors:
  - Hypertension
  - Hyperlipidaemia
  - Diabetes
  - Cigarette smoking
  - Excess alcohol
  - Obesity

Think about the future. Maintain your brain today.
http://www.alz.org/maintainyourbrain/overview.asp

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