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# Alzheimer's Disease and other dementias

Art by Alethea Lacas

## FOCUS ON MILD TO MODERATE ALZHEIMER'S DISEASE

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## ON THE COVER

### *Backgammon,* by Alethea Lacas

Backgammon is a game my grandfather played all his life. Even when he started forgetting the names of his grandchildren and the days of the week, he could still sit down and play his childhood game. The day he forgot how to play, my dad cried.

## We'd Like to Hear From You!

*The Canadian Review of Alzheimer's Disease and Other Dementias* welcomes letters from its readers. Address all correspondences to Letters, *The Canadian Review of Alzheimer's Disease and Other Dementias,* 955 Boul. St. Jean, Suite 306, Pointe Claire, Quebec, H9R 5K3. *The Review* also accepts letters by fax or electronic mail. Letters can be faxed to 514-695-8554 and address electronic mail to alzheimer@sta.ca. Please include a daytime telephone number. Letters may be edited for length or clarity.


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# Seeing Dementia From All Angles

*by Serge Gauthier, MD, FRCPC*

This issue of *The Canadian Review of Alzheimer's Disease and Other Dementias* illustrates the current emphasis on studying these conditions across stages of disease (at-risk, mild symptoms, established dementia) and from the point of view of non-pharmacologic as well as pharmacologic treatments. Furthermore, it merges very well the perspectives of three clinicians, a caregiver and a basic scientist.

The excellent review by Dr. Richard Camicioli on the differential diagnosis of dementia should not discourage clinicians since, with adequate information from patients and informants, they can usually distinguish normal cognition from dementia, and then determine the most likely causes based on age of onset and patterns of progression. After all, Alzheimer's disease (AD) diagnosed after the age of 75 years, with or without cerebrovascular disease, is the most common etiology of dementia in Canada. After meeting in Montreal this March, the participants of the Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDT3) are finalizing their recommendations, to be published later this year.

The review on MCI by Dr. Howard Chertkow is practical and evidence-based. It appropriately highlights the importance of non-pharmacologic interventions. Of note is cognitive training being developed at the *Institut Universitaire de Gériatrie de l'Université de Montréal*, under the leadership of Dr. Sylvie Belleville: the pilot studies are promising and randomized clinical trials are now being planned to prove efficacy. The MCI concept may prove particularly useful as a prodromal stage of AD, allowing for disease-modification treatments when pathology is still reversible.

The four abstracts from the Geneva/Springfield Symposium are of interest because they cover a spectrum of interventions in AD: diet, control of vascular risk factors and cholinesterase inhibitors.

The case study from Dr. Paul Coolican illustrates a common combination of mild depression and early dementia. The Montreal Cognitive Assessment (MoCA; available online at *www.mocatest.org*) would have been a useful complement to the MMSE for this highly educated woman, who needed to be treated with a serotonin-selective reuptake inhibitor (SSRI) such as sertraline or citalopram, and followed over time for changes in mood, cognition and autonomy. Once mild dementia has been clinically diagnosed, the SSRI can be combined with a cholinesterase inhibitor.

Roberta Bedard's personal article offers insight into a caregiver's thoughts and feelings at the time of death of a loved one, usually (as in this case) from aspiration pneumonia. Thank you Roberta for sharing this pain with us.

In the final section, Dr. Jack Diamond, Scientific Director of the Alzheimer Society of Canada, shares his ideas in distinguishing normal aging from AD: not the same! These and other important facts about AD will be reviewed at the 2006 National Conference in Toronto next November. I look forward to seeing you all there!

# Distinguishing Different Dementias

Diagnosing dementia, and its many types, can be challenging for physicians. Patients can exhibit a broad range of symptoms which can overlap with other age-related disorders. Diagnosis is, of course, the important first step in treating and managing dementia. This article reviews diagnostic criteria for the most common dementias, as well as their differential features.

*by Richard Camicioli, MD, FRCPC*

## Introduction

Alzheimer's disease (AD) is the most common dementia, accounting for the majority of cases in the elderly. Differentiation of AD from other common dementias is important in order to implement an appropriate treatment plan and to provide prognostic information for patients and their families.

Criteria for distinguishing types of dementias include: demographics, risk factors, clinical course, examination features and laboratory findings. Complicating the differential diagnosis of dementia is the fact that neurodegenerative and other age-related disorders (such as ischemic disease) can overlap. Also, advanced dementias may resemble each other. In a minority of cases, an accurate diagnosis cannot be made in living patients. This highlights the importance of obtaining an autopsy for deceased dementia patients. This article first reviews diagnostic criteria for the most common dementias (see Table 1, Figure 1) and briefly discusses the differential features of various dementias (see Table 2).

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## Common Dementias

AD is characterized by an insidious onset of progressive impairment of memory, as well as other areas of cognition, including orientation, language, visuospatial function and praxis.[1] Personality change and marked impairment in attention and executive function raise, however, the possibility of other causes of dementia, such as the frontotemporal dementias (FTDs).[2] Occasionally, AD presents with focal features.[3] Marked early motor impairment, including abnormal gait, while common in the later stage of AD,[4] is unusual in the early stage of AD and raises the possibility of vascular dementia (VaD) or dementia with Lewy bodies (DLB). Diagnostic criteria are available for VaD,[5,6] DLB,[7] and FTD but are still being developed for Parkinson's disease with dementia (PDD).[8,9]

***Vascular dementia.*** VaD, dementia caused by cerebrovascular disease, is the second most common form of dementia, accounting for 10% to 20% of cases of dementia in the elderly. "Pure" VaD is relatively uncommon. VaD can be caused by multiple cerebral infarctions, which can be cortical (the left angular gyrus, the frontal lobes and the medial temporal lobes) or subcortical (thalamus, genu of the internal capsule, and caudate nucleus), single strategic infarctions, or diffuse white matter disease.

Cerebrovascular disease is a risk factor for AD, but can also coexist with AD.[10] In fact, a combination of AD and cerebrovascular disease is more likely than VaD. An acute onset, stepwise decline, focal neurological signs, gait impairment and urinary difficulties are suggestive of VaD, especially in the setting of vascular risk factors. Cerebrovascular events can, however, be clinically silent and dementia can progress insidiously.[11]

The Hachinski Scale and the National Institute of Neurological Disorders and Stroke Association –*Association Internationale pour l'Enseignement en Neurosciences* (NINDS-AIREN) criteria are specific to identifying multi-infarct dementia, but are insensitive.[12,13] The California Alzheimer Disease Diagnosis and Treatment Centers (ADDTC) criteria,[5] and Mayo Clinic criteria[14] have improved sensitivity and reasonable specificity.

The term "subcortical dementia," first described in progressive supranuclear palsy (PSP) refers to a dementia where cognitive slowing, apathy, executive dysfunction and pseudobulbar palsy are prominent features in the absence of "cortical" dementia features (aphasia, apraxia and agnosia). Recent studies, comparing cognitive impairment between subcortical VaD and AD, have found that patients with vascular cognitive impairment have relative sparing of memory and worse executive function compared to AD,[15] though imaging changes can overlap with normals.[16]

***Parkinson's disease dementia and dementia with Lewy bodies.*** Cortical Lewy bodies are found in both PDD and DLB. In PDD, parkinsonism precedes cognitive changes by one year or longer, whereas in DLB, dementia and parkinsonism co-occur within a year of each other. Both can exhibit coexistent AD pathology, which influences the clinical presentation.

Table 1

## Non-AD Dementias

**Vascular Dementia**
- Multi-infarct dementia
  - cortical
  - sub-cortical
- Subcortical vascular dementia
- Strategic infarct-related dementia
- Mixed dementia: Alzheimer/Vascular
- Amyloid angiopathy
- Hereditary vascular dementias
  - cerebral autosomal dominant arteriopathy with subcortical ischemic leukoencephalopathy (CADASIL)

**Dementia with Lewy Bodies**
- Dementia with Lewy bodies (DLB)
  - pure DLB
  - mixed Alzheimer/DLB
- Parkinson's disease with dementia

**Frontotemporal dementia**
- Behavioral variant
- Progressive non-fluent aphasia
- Semantic dementia
- Frontotemporal dementia with motor neuron disease

**Other focal neurodegenerative syndromes**
- Progressive apraxia
  - corticobasalganglionic degeneration
  - Alzheimer's disease
- Progressive visuospatial impairment
  - Alzheimer's disease
  - subcortical gliosis
  - Creutzfeld Jakob disease

**Toxins**
- Alcohol

**Normal Pressure Hydrocephalus**

**Dementia related to structural pathology**
- malignant tumors
- benign tumors (depends on location)
- absesses

**Inflammatory disorders**
- Multiple sclerosis
- Vasculitis
  - with systemic involvement
  - without systemic involvement
- Systemic lupus erythematosis
- Sjogren's syndrome
- Sarcoidosis
- Bechet's disease
- Non-vasculitic autoimmune encephalomyelitis (NAIM)

**Infection-related dementias**
- Creutzfeldt Jakob disease
- HIV-related dementia
- Syphillis
- Whipple's disease
- Herpes encephalitis and other viral encephalitides
- Chronic meningitis
- Progressive multifocal leukoencephalopathy
- Subacute sclerosing panencephalitis

**Metabolic-related dementias**
- B12 deficiency
- Thyroid disease
- Parathyroid disease

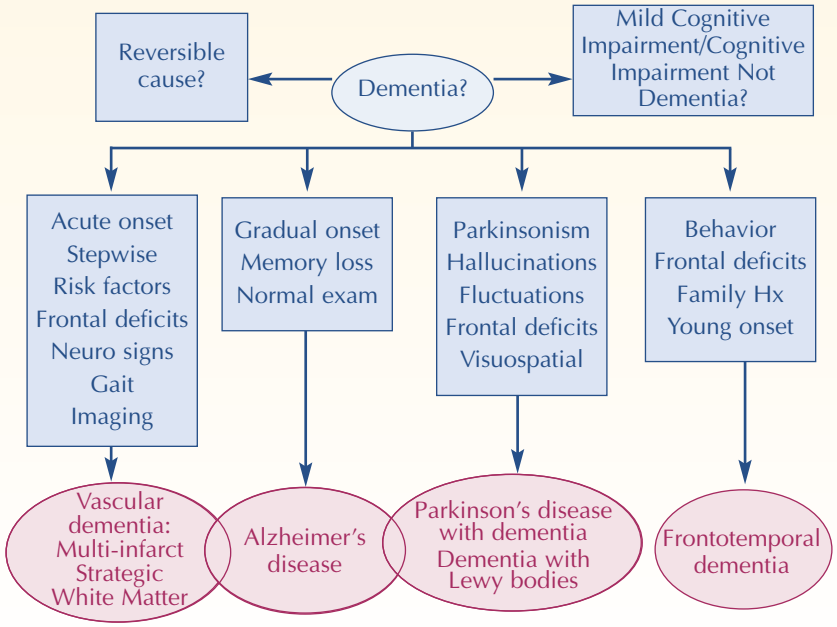
**Hereditary dementias**

Diagnostic features of DLB include visual hallucinations, fluctuating cognition and parkinsonism; two of these three features must be exhibited for a diagnosis of probable DLB, while one of these exhibited features is sufficient for a diagnosis of possible DLB. Sensitivity might be improved by considering secondary symptoms such as syncope, falls, psychosis and visuospatial problems on examination.[17]

Patients with Parkinson's disease develop dementia at a rate of up to 10% per year,[18] with a prevalence of 20% to 30%.[19] PDD and DLB

Figure 1

Differential Diagnostic Consideration for Common Dementias




patients exhibit attention, executive and visuospatial impairment.[7] Sleep disturbance, specifically rapid-eye-movement sleep disorder, is strongly associated with synuclein pathology, including diffuse Lewy bodies.[7] Hallucinations and fluctuations are more common in DLB, but occur in PDD, and are more common in DLB than in AD.[7] Although extra-pyramidal signs may be less severe in DLB compared with PDD, response to levodopa may be better in PDD.[7]

***Frontotemporal dementias***. FTDs are characterized by behavioral and personality changes and cognitive deficits predominantly affecting executive function and language. Compared with AD, FTD patients exhibit a greater degree of behavioral and executive impairment with relative sparing of episodic memory and visuospatial function.[20] Behavioral difficulties including decreased insight, decreased attention to personal care, disinhibition, and inappropriate behavior are prominent in behavioral variant FTD, but also occur in other subtypes of FTD.[21] Language problems seen in FTD variants—primary progressive aphasia and semantic dementia—occasionally lead to diagnostic confusion. Diverse clinical presentations can be imperfectly matched to a variety of pathologies that include tau-positive (ballooned neurons, Pick bodies) or tau-negative changes (ubiquitin-positive inclusions or neuronal loss with gliosis).[22] Tau-negative, ubiquitin-positive inclusions are seen in FTD and in motor neuron disease.

***Normal pressure hydrocephalus (NPH)***. NPH is a potentially treatable syndrome defined by dementia and associated with gait impairment and urinary urgency or incontinence.[23] If one suspects NPH, differential diagnostic considerations include obstructive hydrocephalus, multiple system atrophy (associated with ataxia and incontinence) and vascular dementia with gait impairment. The clinical triad, along with hydrocephalus on imaging, is predictive of shunt responders.[24] Clinical features associated with a positive response include a shorter duration of illness, lack of cortical cognitive deficits and positive response to removal of cerebrospinal fluid, by external or internal lumbar drainage, or by single or repeated lumbar puncture. While duration of cognitive impairment and other features predict poor response, patients may respond despite negative predictors.

## Clinical Features and Differential Diagnosis

***Age of onset***. Age of onset can help in the differential diagnosis of dementia. In a study, Huntington's disease (HD) was the most prevalent cause of dementia in people aged 45 to 65 years, with 18 cases per 100,000, followed by AD and FTD which both had a prevalence of 15 cases per 100,000.[25] VaD accounted for 8.2 cases and DLB accounted for 6.9 cases per 100,000. A second study found that AD was most common with 41 cases per

100,000, followed by 17.9 cases of VaD, 15.4 cases of FTD and 13.6 cases of alcohol-related dementia per 100,000.[26] Futhermore, a study of people aged 65 years and older found the proportion of dementias to be: AD 31.3%; VaD 21.9%; DLB 10.9% and FTD 7.8%.[27] This is also consistent with a Finnish study of people aged 75 years and older.[28] In addition, early-onset adult dementias can occur due to a genetic or metabolic disorder of childhood onset presenting with a later onset.[29-31]

***Family history.*** The presence of a family history can provide clues to the etiology of dementia. While familial AD is well-known, a family history of dementia is even more likely in FTD. The most common definable inheritance pattern in FTD is autosomal dominant, occurring in 10% to 20% or more of cases, depending on the population studied.[32] Family history without a clear inheritance pattern is also common, and can be found in up to 40% of cases. HD is common among early-onset dementias associated with an autosomal dominant family history. A family history is common in AD, and can also occur in DLB. A positive family history is less common in VaD, except in the autosomal dominant VaDs such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).

Table 2

Neurologic Features and Selected Differential Dementia Diagnoses

**Cranial Nerve Findings**
- Whipple's disease
- Progressive supranuclear palsy
- Nieman Pick Type C

**Pyramidal signs**
- Amyotrophic lateral sclerosis
- Vascular cognitive impairment/dementia
- Hereditary spastic paraplegia with dementia
  - familial Alzheimer's disease with spastic paraplegia
- Leukodystrophies
  - adrenoleukodystrophy
  - metachromatic leukodystrophy
  - orthochromatic leukodysrophy
  - Krabbe disease
  - Pelizaeus-Merzbacher disease

**Parkinsonism**
- Early/late
- Parkinson's disease and dementia
- Dementia with Lewy bodies
- Progressive supranuclear palsy
- Alzheimer's disease
- Frontotemporal dementia

**Ataxia**
- Creutzfeld Jakob disease
- Celiac disease
- Hashimoto encephalitis
- Multiple system atrophy
- Spinocerebellar degeneration
- Alcohol

**Apraxia**
- Corticobasal ganglionic degeneration
- Alzheimer's disease

**Gait impairment**
- Vascular cognitive impairment/dementia
- Normal pressure hydrocephalus

**Neuropathy**
- HIV
- Creutzfeld Jakob disease
- Paraneoplastic Syndromes
- Vitamin B12 deficiency
- Alcohol
- Inflammatory disorders
  - Sarcoidosis
  - Sjogren's syndrome
  - Systemic lupus erythematosis
- Hereditary neuropathy with dementia
  - leukodystrophies
  - mitochondrial disorders
  - polyglucosan body disease

**Seizures/Myoclonus**
- Creutzfeldt Jakob disease
- Late Alzheimer's disease
- Whipple's disease

**Metabolic disorders (with seizure and myoclonus)**
- Mitochondrial encephalopathies
- Baltic myoclonus (Unverricht Lundborg disease)
- Lafora disease
- Ceroid lipofuscinosis
- Sialidosis
- GM2 gangliosidosis

## Clinical Course

***Acute onset.*** An acute onset may be consistent with VaD. Delirium should be considered when there is an acute onset associated with fluctuations in level of consciousness, especially in the setting of an underlying cause. Dramatic fluctuations in the level of consciousness are characteristic of DLB.[7] Delirium and dementia commonly co-occur; and are risk factors for each other.[33]

***Rapidly progressive dementias and Creutzfeldt Jakob disease (CJD).*** A rapidly progressive dementia raises the possibility of CJD, but can be seen in AD and DLB as well.[34] CJD is a rapidly progressive dementia that can only be definitively diagnosed by a brain tissue examination showing prion proteins with associated spongiform changes. It is a reportable disease in Canada (visit *www.phcaspc.gc.ca/hcaiiamss/-cjdmcj/index.html*). CJD can be sporadic, familial or transmissible. Transmissible forms of CJD include iatrogenic and variant CJD. Criteria for probable CJD include typical electroencephalogram (EEG) features with at least two of the following: myoclonus, visual or cerebellar signs, pyramidal or extra-pyramidal signs, or akinetic mutism (visit *www.eurocjd.ed.ac.uk/-def.html*). Clinical diagnosis can also be made with a history of a rapidly progressive dementia with duration of less than 2 years, and at least two clinical features, with a positive 14-3-3 test on cerebrospinal fluid (CSF) examination. False positives on the 14-3-3 test include AD, VaD and encephalitis. False negatives can also be seen, especially in slowly progressive CJD.[35] Diffusion-weighted magnetic resonance imaging (MRI) may have superior sensitivity compared with EEG and a CSF examination.[36]

Sporadic CJD is inexorably progressive, usually resulting in death within a year; however, the course can be longer.[37] A long duration is common in familial prion diseases. Variant CJD is a progressive neuropsychiatric disorder ultimately leading to ataxia, dementia and myoclonus (or chorea) without the typical EEG appearance of CJD or the proportion with elevation in the 14-3-3 protein.[38] Young onset sporadic CJD cases have a long neuropsychiatric prodrome.[39]

***Other rapidly progressive dementias.*** Dementia associated with motor neuron disease can also run a rapid course. Syndromes that should be considered in the differential diagnosis of a rapidly progressive dementia include viral encephalitis, paraneoplastic (limbic) encephalitis, central nervous system cancer, Hashimoto's encephalitis, other disorders (including antiphospholipid syndrome, systemic lupus erythematosis, sarcoidosis and non-vasculitic autoimmune meningoencephalitis),[40,41] autoimmune infections and metabolic disorders.

## Clinical and Neurological Exam Features

Weight loss and or other systemic complaints raise the concern of an underlying neoplasm that might directly (metastasis or carcinomatous meningitis) or indirectly (paraneoplastic) lead to cognitive decline. Clues to an acute and subacute central nervous system infection include headache, fever, seizures, systemic complaints, infection of peripheral tissue, rapid progression of symptoms, focal neurological features (abscess with parenchymal involvement) and travel to endemic areas. Specific features such as rash and arthritis raise the concern of infection or autoimmune processes.

***Dementia with motor impairment.*** Supranuclear gaze palsy and a history of early falls are characteristic of PSP, but can be seen in corticobasalganglionic degeneration, which leads to progressive apraxia and FTD.[42] Not all PSP patients exhibit abnormal eye movements. Impaired saccades can be seen in HD, CBDG, PSP and FTD. Also, unusual rhythmic ocular and associated cranial movements—oculomasticatory myorhythmia—are seen in Whipple's disease.[43]

DLB and PDD are characterized by parkinsonism (tremor, bradykinesia, rigidity). Dysfunction of the extra-pyramidal system is evident in HD (chorea), PSP (impaired postural reflexes), CBDG (myoclonus, dystonia) and FTD (parkinsonism). Chorea and peripheral neuropathy are seen in neuroacanthocytosis which can be associated with dementia. Gait disorder is characteristic of NPH and VaD. Pantothenate kinase-associated neurodegeneration, a disorder of brain iron accumulation (seen on MRI) can occur in adults where it can present as a progressive movement disorder with chorea and dementia. In the setting of a younger patient with dementia, dystonia or another movement disorder, Wilson's disease should be excluded given the potential for treatment.

Pyramidal system dysfunction is seen in cerebrovascular disease and associated VaD. Leukodystrophies, in particular adrenoleukodystrophy and metachromatic leukodystrophy, are associated with cognitive decline and spasticity. Vitamin B12 deficiency can lead to a myelopathy with upper motor neuron signs and peripheral neuropathy (decreased ankle jerks and sensory loss).

Mixed upper and lower motor neuron signs are seen in amyotrophic lateral sclerosis (ALS), which is commonly associated with cognitive impairment and less frequently associated with dementia. Conversely, motor neuron disease is also seen in FTD, where it is associated with a worse prognosis.

Cerebellar ataxia may be seen in patients with prion disease. Superficial siderosis causes dementia and progressive neurological deficits, including pyramidal signs and ataxia.[44] Central nervous system microbleeds, which can be identified using T2*-weighted gradient echo MRI scans, are found in amyloid angiopathy,[45] CADASIL and AD. Hereditary ataxia-dementia syndromes include dentatorubral-pallidoluysian atrophy and other spinocerebellar ataxias. Celiac disease, paraneoplastic syndromes, and Hashimoto encephalitis are examples of acquired and potentially treatable ataxia-dementia syndromes. Recently the fragile X premutation has been found to be a relatively common disorder associated with ataxia, tremor, parkinsonism and dementia.[46] Multiple system atrophy is associated with subcortical cognitive deficits.

***Seizures and myoclonus.*** Seizures and myoclonus are relatively rare in dementia patients. Myoclonus is characteristic of CJD, and common in AD, especially late in the course. Focal myoclonus is also evident in CBGD. A number of young-onset dementias are associated with seizures and myoclonus. Recurrent non-convulsive seizures can sometimes be associated with cognitive impairment, mimicking dementia.

## Reversible Dementias

While completely reversible dementias are rare,[47,48] common co-morbid conditions may exacerbate symptoms. Intracranial pathology (*i.e.,* cerebrovascular disease, tumors, and hydrocephalus) is often accompanied by associated signs and a progressive course. Head trauma can usually be identified by history. Seizures, seen in DLB, are associated with fluctuating symptoms. Depression often co-occurs with dementia and depressive symptoms should be treated regardless of whether or not they are considered the primary cause of cognitive impairment. Vitamin B12 deficiency and thyroid disease can be clinically silent except for cognitive impairment. Alcohol is the most common toxin associated with cognitive impairment. Rarer entities, including autoimmune disorders, can cause dementia syndromes.

HIV is associated with a subcortical dementia and is an important consideration, especially in individuals with risk factors or known HIV.[49] Neurosyphilis remains an important cause of dementia to identify because it is potentially treatable.[50] Viral encephalitis can present in an indolent fashion, unpredictably leaving dementia patients. Furthermore, worldwide tuberculosis and neurocysticercosis are common infections that have a predilection for the central nervous system. Lyme disease is an infection associated with dementia that should be considered in individuals with appropriate symptoms, such as a rash and polyarthritis, from an endemic area. Immunosupression predisposes to infections in general, and specific disorders, such as progressive multifocal leukoencephalopathy, are important to consider in this setting.

## Laboratory Investigations

Guidelines exist for the evaluation of dementia.[51,52] It is important to rule out anemia, renal or hepatic dysfunction, electrolyte abnormalities, and abnormal glucose, as these problems can interfere with cognitive function. Most recommendations include checking a vitamin B12 level and thyroid function since these can be associated with

insidious cognitive decline. Calcium or phosphate abnormalities raise the concern of parathyroid dysfunction, which is associated with cognitive impairment, parkinsonism and depression.

***Neuroimaging.*** Mass lesions and hydrocephalus are identified by imaging. White matter changes lead to circumscribed diagnostic considerations. Contrast enhancement raises the possibility of infiltrative, infectious or inflammatory disorders. While AD is associated with medial temporal atrophy compared to controls, FTD and CBDG are associated with asymmetric or frontal atrophy on computed tomography (CT) or MRI scans or perfusion deficits on single photon emission computed tomography (SPECT) and metabolic deficits on positron emission tomography (PET) scans.[53] PSP patients have midbrain and frontal atrophy.

***Lumbar puncture***. Specific tests, including CSF examination, are useful in the appropriate clinical setting. This should prompt investigations targeted by the clinical picture. Infections have abnormalities on CSF examination, including elevated protein, pleiocytosis and evidence for microorganism on examination or culture. The polymerase chain reaction is useful for amplifying genomic material for specific infections, including herpes simplex and Whipple's disease. While elevation in peripheral anti-neuronal bodies (*i.e.,* anti-Hu, anti-Yo) may be found in paraneoplastic syndromes, these may be absent; hence a targeted assessment for cancer is a first step in evaluating patients with a suspected paraneoplastic syndrome.[54] Of note, limbic encephalitis can have an autoimmune basis in the absence of a neoplasm. Inflammatory disorders of the brain often lead to elevated protein and may lead to elevated cell counts. Multiple sclerosis and other inflammatory disorders can lead to an elevated immunoglobulin index and oligoclonal bands. Serum or CSF angiotensin-converting enzyme can be elevated in sarcoidosis.

***Peripheral biopsy***. Skin and muscle biopsy may be helpful in some dementias and may obviate a brain biopsy if diagnostic. Skin changes may be evident in some dementias such as Sneddon's syndrome. Vasculitis may be evident in skin or muscle biopsy. An angiopathy characteristic of CADASIL can be diagnosed on skin biopsy and might be pursued in rapidly progressive dementia with white matter disease.[55] Skin biopsy can be helpful in the diagnosis of ceroid lipofuscinosis or Lafora's disease, young-onset disorders associated with dementia. Polyglucosan body disease is a disorder associated with urinary incontinence, gait impairment and neuropathy, with periodic acid-Schiff (PAS) positive inclusions on nerve or sweat gland biopsy. Salivary gland biopsies are helpful in diagnosing Sjogren's syndrome.

***Brain biopsy.*** Brain biopsy is reserved for cases where there is diagnostic uncertainty and is particularly important in cases where therapeutics may be instituted or altered on the basis of a biopsy.[56] Biopsies may be complicated by seizures, delirium, pneumonia and wound infections. Diagnoses that might lead to specific treatments include: inflammatory disorders, including vasculitis, sarcoidosis, or non-vasculititic autoimminune meningoencephalitis. Parenchymal or perivascular infiltrative disorders may also be diagnosed definitively via brain biopsy. Whipple's disease and infections by other fastidious organisms can sometimes be diagnosed by biopsy alone. While the identification of a non-treatable degenerative syndrome can often assist families in decision making, justifying brain biopsies in some atypical or rapidly progressive cases, biopsies are often non-specific—43% in a study by Warren et al.[56]

## Summary

In summary, physicians conducting a careful clinical approach should differentiate typical AD from other dementias. Of course, diagnostic uncertainty will remain in a minority of cases. The challenge in such a situation, is to identify diagnoses for patients for which there are treatments available.

References
1. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurolog 1984;34(7):939-44.
2. Galton CJ, Patterson K, Xuereb JH, et al. Atypical and typical presentations of Alzheimer's disease: a clinical, neuropsychological, neuroimaging and pathological study of 13 cases. Brain 2000;123 (Pt 3):484-98.
3 Duffy CJ. Posterior cortical atrophy: Lost but not forgetting. Neurology 2004: 63; 1148-9.
4. Allan LM, Ballard CG, Burn DJ, et al. Prevalence and Severity of Gait Disorders in Alzheimer's and Non-Alzheimer's Dementias. J Am Geriatr Soc 2005;53(10):1681-7.
5. Chui HC, Victoroff JI, Margolin D, et al. Criteria for the diagnosis of Ischemic vascular dementias proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centres. Neurology 1992;42(3 Pt 1):473-80.
6. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 1993; 43(2):250-60.
7. McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology. Dec 27 2005;65(12):1863-1872.
8. McKhann GM, Albert MS, Grossman M, et al. Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. Arch Neurol 2001; 58(11):1803-9.
9. Camicioli R, Fisher N. Progress in clinical neurosciences: Parkinson's disease with dementia and dementia with Lewy bodies. Can J Neurol Sci 2004;31(1):7-21.
10. Snowdon DA, Greiner LH, Mortimer JA, et al. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. JAMA 1997;277(10):813-7.
11. Vermeer SE, Prins ND, den Heijer T, et al. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 2003;348:1215-22.
12. Moroney JT, Bagiella E, Desmond DW, et al. Meta-analysis of the Hachinski Ischemic Score in pathologically verified dementias. Neurology 1997;49(4):1096-105.
13. Pohjasvaara T, Mantyla R, Ylikoski R, et al. Comparison of different clinical criteria (DSM-III, ADDTC, ICD-10, NINDS-AIREN, DSM-IV) for the diagnosis of vascular dementia. National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences. Stroke 2000;31(12):2952-7.
14. Knopman DS, Parisi JE, Boeve BF, et al. Vascular dementia in a population-based autopsy study. Arch Neurol 2003; 60(4):569-75.
15. Graham NL, Emery T, Hodges JR. Distinctive cognitive profiles in Alzheimer's disease and subcortical vascular dementia. J Neurol Neurosurg Psychiatry 2004; 75(1):61-71.
16. Ballard CG, Burton EJ, Barber R, et al. NINDS AIREN neuroimaging criteria do not distinguish stroke patients with and without dementia. Neurology. Sep 28 2004;63(6):983-988.
17. Merdes AR, Hansen LA, Jeste DV, et al. Influence of Alzheimer pathology on clinical diagnostic accuracy in dementia with Lewy bodies. Neurology 2003; 60(10):1586-90.
18. Aarsland D, Andersen K, Larsen JP, et al. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch Neurol 2003; 60(3):387-92.
19. Miyasaki JM, Shannon K, Voon V, et al. Practice Parameter: Evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006:66(7):996-1002.
20. Knopman DS, Boeve BF, Parisi JE, et al. Antemortem diagnosis of frontotemporal lobar degeneration. Ann Neurol 2005; 57(4):480-8.
21. Kertesz A, Nadkarni N, Davidson W, et al. The Frontal Behavioral Inventory in the differential diagnosis of frontotemporal dementia. J Int Neuropsychol Soc. May 2000;6(4):460-468.
22. Hodges JR, Davies RR, Xuereb JH, et al. Clinicopathological correlates in frontotemporal dementia. Ann Neurol 2004;56(3):399-406.
23. Hebb AO, Cusimano MD. Idiopathic normal pressure hydrocephalus: a systematic review of diagnosis and outcome. Neurosurgery 2001;49(5):1166-84.
24. Vanneste J, Augustijn P, Tan WF, et al. Shunting normal pressure hydrocephalus: the predictive value of combined clinical and CT data. J Neurol Neurosurg Psychiatry 1993; 56(3):251-6.
25. Ratnavalli E, Brayne C, Dawson K, et al. The prevalence of frontotemporal dementia. Neurology 2002; 58(11):1615-21.
26. Harvey RJ, Skelton-Robinson M, Rossor MN. The prevalence and causes of dementia in people under the age of 65 years. J Neurol Neurosurg Psychiatry 2003; 74(9):1206-9.
27. Stevens T, Livingston G, Kitchen G, et al. Islington study of dementia subtypes in the community. Br J Psychiatry 2002; 180:270-6.
28. Rahkonen T, Eloniemi-Sulkava U, Rissanen S, et al. Dementia with Lewy bodies according to the consensus criteria in a general population aged 75 years or older. J Neurol Neurosurg Psychiatry 2003; 74(6):720-4.
29. Sampson EL, Warren JD, Rossor MN. Young onset dementia. Postgrad Med J. Mar 2004;80(941):125-39.
30. Coker SB. The diagnosis of childhood neurodegenerative disorders presenting as dementia in adults. Neurology 1991; 41(6):794-8.
31. Gray RG, Preece MA, Green SH, et al. Inborn errors of metabolism as a cause of neurological disease in adults: an approach to investigation. J Neurol Neurosurg Psychiatry 2000; 69(1):5-12.
32. Chow TW, Miller BL, Hayashi VN, et al. Inheritance of frontotemporal dementia. Arch Neurol 1999; 56(7):817-22.
33. McCusker J, Cole M, Dendukuri N, et al. Delirium in older medical inpatients and subsequent cognitive and functional status: a prospective study. CMAJ 2001; 165(5):575-83.
34. Tschampa HJ, Neumann M, Zerr I, et al. Patients with Alzheimer's disease and dementia with Lewy bodies mistaken for Creutzfeldt-Jakob disease. J Neurol Neurosurg Psychiatry 2001; 71(1):33-9.
35. Geschwind MD, Martindale J, Miller D, et al. Challenging the clinical utility of the 14-3-3 protein for the diagnosis of sporadic Creutzfeldt-Jakob disease. Arch Neurol 2003; 60(6):813-6.
36. Young GS, Geschwind MD, Fischbein NJ, et al. Diffusion-weighted and fluid-attenuated inversion recovery imaging in Creutzfeldt-Jakob disease: high sensitivity and specificity for diagnosis. AJNR Am J Neuroradiol 2005; 26(6):1551-62.
37. Brown P, Rodgers-Johnson P, Cathala F, et al. Creutzfeldt-Jakob disease of long duration: clinicopathological characteristics, transmissibility, and differential diagnosis. Ann Neurol 1984;16(3):295-304.
38. Will RG, Zeidler M, Stewart GE, et al. Diagnosis of new variant Creutzfeldt-Jakob disease. Ann Neurol. May 2000;47(5):575-82.Brown P, Rodgers-Johnson P, Cathala F, et al. Creutzfeldt-Jakob disease of long duration: clinicopathological characteristics, transmissibility, and differential diagnosis. Ann Neurol 1984;16(3):295-304.
39. Boesenberg C, Schulz-Schaeffer WJ, Meissner B, et al. Clinical course in young patients with sporadic Creutzfeldt-Jakob disease. Ann Neurol 2005; 65(10):1544-50
40. Caselli RJ, Boeve BF, Scheithauer BW, et al. Nonvasculitic autoimmune inflammatory meningoencephalitis: a reversible form of encepha-lopathy. Neurology 1999; 53(7):1579-81.
41. Gomez-Puerta JA, Cervera R, Calvo LM, et al. Dementia associated with the antiphospholipid syndrome: clinical and radiological characteristics of 30 patients. Rheumatology (Oxford). 2005; 44(1):95-9.
42. Litvan I, Bhatia KP, Burn DJ, et al. Movement Disorders Society Scientific Issues Committee report: SIC Task Force appraisal of clinical diagnostic criteria for Parkinsonian disorders. Mov Disord 2003;18(5):467-86.
43. Louis ED, Lynch T, Kaufmann P, et al. Diagnostic guidelines in central nervous system Whipple's disease. Ann Neurol 1996;40(4):561-8.
44. .Fearnley JM, Stevens JM, Rudge P. Superficial siderosis of the central nervous system. Brain 1995;118( Pt 4):1051-66.
45. Remes AM, Finnila S, Mononen H, et al. Hereditary dementia with intracerebral hemorrhages and cerebral amyloid angiopathy. Neurology 2004; 63(2):234-40.
46. Hall DA, Berry-Kravis E, Jacquemont S, et al. Initial diagnoses given to persons with the fragile X associated tremor/ataxia syndrome (FXTAS). Neurology 2005; 65(2):299-301.
47. Hejl A, Hogh P, Waldemar G. Potentially reversible conditions in 1000 consecutive memory clinic patients. J Neurol Neurosurg Psychiatry 2002; 73(4):390-4.
48. Clarfield AM. The decreasing prevalence of reversible dementias: an updated meta-analysis. Arch Intern Med 2003; 163(18):2219-29.
49. McArthur JC, Brew BJ, Nath A. Neurological complications of HIV infection. Lancet Neurol 2005; 4(9):543-55.
50. Timmermans M, Carr J. Neurosyphilis in the modern era. J Neurol Neurosurg Psychiatry 2004; 75(12):1727-30.
51. Petersen RC, Stevens JC, Ganguli M, et al. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001; 56(9):1133-42.
52. Patterson C, Gauthier S, Bergman H, et al. The recognition, assessment and management of dementing disorders: conclusions from the Canadian Consensus Conference on Dementia. Can J Neurol Sci 2001; 28 Suppl 1:S3-16.
53. Talbot PR, Lloyd JJ, Snowden JS, et al. A clinical role for 99mTc-HMPAO SPECT in the investigation of dementia? J Neurol Neurosurg Psychiatry 1998; 64(3):306-13.
54. Graus F, Delattre JY, Antoine JC, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry 2004; 75(8):1135-40.
55. Markus HS, Martin RJ, Simpson MA, et al. Diagnostic strategies in CADASIL. Neurology 2002; 59(8):1134-8.
56. Warren JD, Schott JM, Fox NC, et al. Brain biopsy in dementia. Brain 2005;128(Pt 9):2016-25.

# Treating Mild Cognitive Impairment

The term Mild Cognitive Impairment (MCI) brings to light the recent efforts of physicians to recognize the subtle classifications of normal and abnormal aging. While MCI clinical trials are currently underway, it will be years before their results are known. This article reviews the current status of symptomatic and preventive therapies available for managing MCI, and discusses their efficacy.

*by Howard Chertkow, MD, FRCPC*

Clinicians are becoming increasingly aware of the number of elderly individuals who fall into that borderzone between normality and dementia. While a number of terms have been applied to this group, by far the most common term used is Mild Cognitive Impairment (MCI).[1,2] In 2003, an international working group agreed on general criteria for MCI: the subject was not judged to be normal or demented, the cognitive decline was reported by self and/or informant, there was impairment on objective cognitive tasks and there was evidence of decline over time on such tasks. In addition, there were preserved basic activities of daily living, or else minimal impairment only in complex instrumental functions.[3,4]

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While this article does not address the larger question of whether MCI is a clinical entity that deserves attention, (which has been addressed in a number of articles[5-8]), it does address current therapies for individuals with MCI, and assess their efficacy.

## Reasons to Treat MCI

The first question to ask is: why should we treat MCI? One answer is that the symptom of memory loss is upsetting to some patients. In other words, treatment may be symptomatic because of the individual's concerns over memory loss in MCI. Notice that this level of concern varies from individual to individual. Many patients recruited into a recent MCI trial at our centre stated that they did not feel sick, were not bothered by their memory lapses, and did not require medication. A second reason to treat MCI is to prevent development of future dementia since MCI is a "high-risk" state for future dementia (see Figure 1). A third reason to treat MCI subjects is that in fact many of the individuals with MCI already have significant early Alzheimer's disease (AD) pathology[9,10] and with time the majority of members of any MCI cohort will progress to AD. In this sense we are not attempting treatment to prevent AD, so much as treating to modify and slow the disease at its earliest presentation.

While accepting the above, it must be emphasized that MCI is heterogeneous, and not all MCI individuals (at least in our experience and that of others) progress to AD.[11-13] Therefore in some cases, one would be treating individuals to prevent progression, who would not in fact have progressed. Thus, the "risk:benefit" ratio for treating MCI differs from that of AD. The bar for acceptable medications must therefore be set higher. The question is not whether we should treat, but what should constitute current recommended therapy.

## Cognitive Training and Stimulation

Let us first look at non-pharmacologic approaches. There are intriguing hints in the normal elderly that

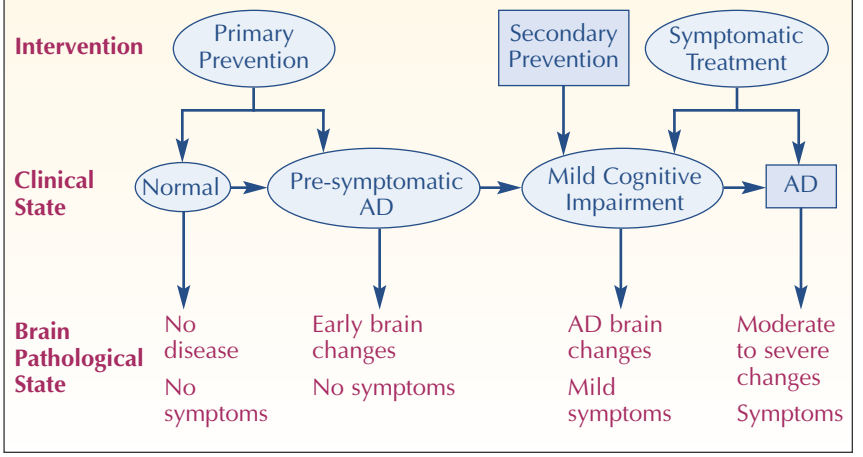
engagement in stimulating cognitive activities is associated with better memory and verbal abilities.[14] Case control and longitudinal studies have shown that participation in intellectually stimulating and social activities in midlife was associated with reduced risk of developing AD.[15,16] What about randomized controlled trials (RCTs) of cognitive stimulation? A number of studies have shown that memory training improved performance on targeted memory tasks and that the effect sizes for the training effects were in the moderate range and were sustained over a two-year follow-up.[17,18] We do not know, however, if such interventions would in any way prevent or decrease dementia.

Several open and randomized controlled trials have been reported on the effect of cognitive training and intervention in MCI.[19,20] These studies provide encouraging findings of benefit, but there are many questions remaining.[21,22] The effort required to implement cognitive training on a large scale is not trivial, and before widespread recommendation of this therapy can occur, more replication studies are required with properly controlled RCT designs, larger sample sizes, and analyses that control for Type 1 error.

Thus, the evidence at the present time is insufficient to conclude that organized cognitive intervention is beneficial in preventing progression in MCI or warrants prescription. On the other hand, given that there is little or no "down-side" to cognitive activity, it is reasonable for physicians and therapists to promote engagement in cognitive activity as part of an overall "healthy lifestyle" formulation for elderly individuals with and without memory loss.

Figure 1

Classes of Therapy in MCI and AD




## Physical Training

The situation with physical training and exercise is quite similar. Several longitudinal cohort studies carried out in normal elderly individuals indicate that physical exercise is associated with reduced cognitive decline and reduced risk of dementia.[23,24] However, there are also studies that failed to find a protective effect of physical exercise on cognitive decline and on incident dementia.[16] Two recent meta-analyses have been published regarding the impact of physical exercise programs on the cognitive function of older adults.[25,26] Both meta-analyses reported moderate effect sizes for the exercise training effect on global cognitive scores and executive control. There are important implications of such research in terms of potential public health measures to prevent dementia and cognitive decline. More studies are needed to assess the optimal exercise training modalities in older adults, particularly in terms of intensity and duration. No studies have been carried out specifically with MCI persons to assess the effect of physical training on their cognitive capacities and cognitive decline.

Keeping this in mind, the Third Canadian Consensus Conference on Diagnosis and Treatment of Dementia recommended that physicians and therapists may promote physical activity at an intensity level that is adapted to the persons' overall physical capacities, as part of a "healthy lifestyle" for older individuals with and without memory loss.[27]

## Treatment of Exacerbating and Co-morbid Conditions

There are a series of other conditions that can exacerbate memory loss in MCI, or even produce MCI in an otherwise cognitively normal elderly individual. Attention to these factors is recommended, even in the absence of formal RCTs.

***There are a series of other conditions that can exacerbate memory loss in MCI, or even produce MCI in an otherwise cognitively normal elderly individual. Attention to these factors is recommended, even in the absence of formal RCTs.***

For instance, it is increasingly clear that stress, via cortisol levels, acts as a direct toxin on the hippocampus, capable of amplifying disease-related hippocampal dysfunction.[28-30] Recent studies on emotional factors such as proneness to distress show this to be a significant risk factor for AD.[31] Attempts to reduce stress levels in MCI seem a reasonable goal. Although there have not been direct clinical studies, untreated depression will exacerbate and amplify memory loss.[35-39]

An important study in the Kungsholmen district of Stockholm demonstrated that a poor or limited social network increased the risk of dementia by 60% and a significant gradient was found for increasing degrees of social connections It appears that an extensive social network seems to protect against dementia.[40] Clearly this requires a lifelong commitment to building social interactions, but this may be a modifiable risk, and social interaction can be encouraged in MCI individuals.

Also, patients with sleep disorders often present with memory loss, and this seems a reasonable factor to modify and control.[32-34] Assessment and treatment of sleep apnea in MCI patients is recommended if there is a sleep complaint.

## Symptomatic Therapy

There is no current treatment for MCI sufficiently substantiated to have obtained government approval from FDA or Canadian government regulators. This contrasts with the situation in Europe, where medications such as Ginkgo biloba and hydergine have been approved broadly for "memory impairment." While some reviews have tended to be fairly positive about treatment effects,[41] symptomatic therapy is generally found to be disappointing, although the occasional patient appears to have a significant improvement on each of the medications listed in Table 1.

***Cholinesterase inhibitors.*** The three available cholinesterase inhibitors (CIs) in North America—donepezil, rivastigmine and galantamine—are approved for treatment of mild to moderate AD, not MCI. These all produce modest improvement and stabilization in the majority of patients.[42,43]

Symptomatic treatment of the memory complaints in MCI with CIs is generally disappointing. Clinicians have anecdotally reported that certain MCI patients benefit from treatment with CIs in terms of memory and global function. Salloway et al studied 270 patients across 20 centres meeting criteria for amnestic MCI.[45] Half were treated with donepezil 10 mg for six months and a series of cognitive and global tests were administered. Two thirds of the donepezil-treated cohort completed the study, and change in a paragraph recall test as well as the Clinical Global Impression of Change-MCI instrument were used as the primary outcome measures. Neither of these measures showed significant beneficial effects of therapy at the end of six months. However, a major secondary measure, the ADAS-Cog, did show a symptomatic benefit. Subjectively, patients treated with donepezil reported greater improvement in memory function than those given placebo. They reported feeling sharper mentally, more organized, and more confident of their memory. All of this suggests that at least some MCI individuals will have a significant clinical benefit from CIs, but overall the effects are mild. The recent

Canadian Consensus Conference on dementia therapy did not recommend CIs as therapy in MCI.[27]

***Ginkgo biloba.*** At present, Ginkgo biloba is commonly prescribed in Europe for all memory-impaired patients, with the idea that it improves blood and oxygen flow to the brain and supports memory function, mental sharpness and circulation. There are few if any well-designed clinical trials that support this conclusion.[46] There was one placebo-controlled study of Ginkgo biloba in AD, with a high dropout rate. This showed a significant symptomatic benefit in AD, albeit approximately a quarter of the efficacy of CIs.[47] It is notable that in some countries such as Germany, Ginkgo biloba is routinely prescribed for AD because of its greater accessibility and lower cost to patients.

There is an ongoing long-term study testing the hypothesis that Ginkgo biloba, as an anti-oxidant, might prevent onset or slow progression of AD. Data are not yet available. The Canadian Consensus Conference concluded that there is currently fair evidence to recommend against the use of Ginkgo biloba therapy in MCI.

***Nootropics.*** There are a number of over-the-counter "dietary supplements" which have been suggested to strengthen and protect neurons of the brain involved in memory, serving as "memory nutrients." These "nootropics" have non-specific mechanisms of action, with putative effects on energy metabolism, cholinergic mechanisms, excitatory amino acid receptor-mediated functions, as well as hormonal mechanisms.[49] In this class, one would list phosphatidyl-serine (PS), acetyl-l-carnitine and piracetam. These are available through health-food stores as diet supplements, not medications. Evidence of their efficacy is slim, but they have few if any side effects. Presumably, these nootropics would have symptomatic rather than preventive effects in MCI.

PS is obtained from cows and more recently a form derived from soy lecithin is being sold. A PS study from 1991 had subjects with mild memory loss, similar to MCI, taking PS 300 mg for three months. The subjects showed some modest improvement in their memory. The effects tended not to occur in everyone and there was no benefit in AD patients.[50] There have been no serious studies of PS in the past ten years. Piracetam was tested in several studies in individuals who

Table 1
## Symptomatic and Preventive Therapies for MCI

**Symptomatic therapies**

Cholinesterase inhibitors

Ginkgo biloba

Nootropic medications
- phosphatidyl-serine (PS)
- acetyl-L-carnitine,
- choline (phosphatidylcholine, citicoline)
- piracetam

Memory stimulants
- ampakines
- NMDA receptor modulation)
- CREB modulators

**Preventive therapies**

Anti-oxidants
- vitamin E
- other anti-oxidants (selegiline, vitamin C)

Homocysteine

Omega fatty acids

Cholinesterase inhibitors

Anti-inflammatory agents

Estrogen

Statins

Anti-amyloid therapies
- beta- and gamma-secretase inhibitors
- GAG-mimetics

Therapy for vascular risk factors

may have had MCI.[51] There was evidence of mild improvement in memory and attention.

Overall, despite lofty claims for dramatic effects of nootropics, (generally from those involved in marketing of these agents), the proven benefit of each of these agents is modest. One broad review stated in conclusion "All in all, we believe that the current data do not allow strong scientifically based recommendations for any of these memory nutrients (including PS and ginkgo). However, the data also do not allow us to conclude that these nutrients are ineffective in boosting memory."[46]

***At present, Ginkgo biloba is commonly prescribed in Europe for all memory-impaired patients, with the idea that it improves blood and oxygen flow to the brain and supports memory function, mental sharpness and circulation. There are few if any well-designed clinical trials that support this conclusion.[46]***

## Memory Stimulants and Future Smart Drugs

The media have been reporting the "imminent" arrival of medications that will impact the neurochemical processes of memory itself. Such medications have the potential to compensate for the neurochemical deterioration thought to be part of MCI and even AD, without changing or retarding the underlying pathological processes.[52] The candidate drugs directed at improving memory fall into one of two categories: those that target the initial induction of long-term potentiation, and those that target the later stages of memory consolidation. Drug candidates include ampakines which are already beginning to enter Phase II clinical trials for MCI treatment.[53-56] The efficacy and side-effect profiles of these cognitive enhancers are unknown. In the second category we find drugs aimed at increasing CREB (cyclic-AMP response element binding protein), the element-binding protein which in turn activates genes to produce proteins that strengthen the synapse in response to experience—the basis of long-term memory. A number of mechanisms are being explored that can impact on the CREB level.[57] Human trials are still years away.

## Prevention of AD by Intervention at the MCI Stage

The most critical interest from physicians, patients, and the pharmaceutical industry is in pharmacologic interventions that can be instituted at the MCI stage to prevent progression to dementia, specifically AD. Most readers will be aware that no such effective medication currently exists, has been substantiated by multiple or convincing randomized placebo-controlled clinical trials, or is available in pharmacies. There are nine kinds of potential prevention therapies that cannot currently be recommended (see Table 2). These each could theoretically delay or prevent progression to AD from the MCI state, but have failed to reach sufficient strength of evidence to be recommended. The theoretical arguments are based on understanding of AD pathophysiology or evidence from population studies. Studies testing most of these mechanisms are currently underway. It is important to point out, however, that retrospective observational studies are not the same as carefully controlled randomized intervention studies. This has been brought harshly to the forefront by the failure of a number of RCTs to confirm efficacy of interventions derived from epidemiologic studies. In these cases, either the population evidence was simply wrong, or the "critical period" for the pharmacologic intervention was missed, and MCI was simply too late a time to treat. We will mention only one of these, vitamin E, along with positive therapy recommendations for treating vascular risk factors, and perhaps suggesting dietary manipulations.

## Should We Be Using Vitamin E and Anti-oxidants?

Vitamin E, an anti-oxidant, has had a roller-coaster profile as a medication to prevent dementia, and this highlights the challenges and difficulties

Table 2

## Non-recommended Therapies Aimed at Preventing Progression from MCI to AD

| Class | Name of medications | Mechanism of action | Evidence for use | Negative trials |
|---|---|---|---|---|
| Vitamin E | Vitamin E | Reduces oxidative stress | Population studies [61-63], RCT [60] | Meta-analyses [64,65] |
| Alternative anti-oxidants | Vitamins A, C, Gingko biloba | Reduce oxidative stress | As above, also [81] | RCT [64] |
| Vitamins B complex | Vitamins B6, B12, folic acid | Reduce homocysteine levels | Framingham Study [77] | No RCTs as yet |
| Omega fatty acids | Docosahexaenoic acid (DHA) | Role in neuronal communication | Observational studies | No RCTs as yet |
| Cholinesterase inhibitors | Donepezil, rivastigmine, galantamine | Increase synaptic acetylcholine availability | Memory Impairment Study [64] (for ApoE4 carriers) | RCTs [64],[66] |
| Anti-inflammatory agents | Ibuprofen, indomethacin, prednisone | Reduce inflammatory response | Observation study [82] | RCT [83] |
| Estrogen | Estradiol, raloxifene | Multiple mechanisms of action | Observation studies [84,85], RCT [86] | RCTs: WHIMS [87,88] Nurses Health Study [89] |
| Statins | Atorvastatin, five others | Block liver enzyme essential for cholesterol production | Observational studies [90, 91], RCT [92] | No RCTs in MCI as yet |
| Anti-amyloid therapy | GAG-mimetics, immunotherapy | Prevents production (immunotherapy) or aggregation (GAG-mimetics) of A-beta amyloid fragments | Promising RCTs [93,94], but immunotherapy complications (encephalitis) | No RCTs in MCI as yet |

in deriving preventive therapies for a chronic disease like AD. The case for anti-oxidant therapy to prevent onset of AD (as well as other neurodegenerative diseases and aging in general) is relatively strong, and new evidence continues to accumulate, although none reach the level of recommendations for therapy. Oxidative damage can be found in a number of neurodegenerative conditions including AD.[58,59] In a widely cited study of vitamin E in AD,[60] patients taking high-dose vitamin E for up to 24 months reached the functional milestone of institutionalization more slowly than individuals on placebo. The treatment was regarded as safe; vitamin E was not associated with increased risk of death. Indeed, an identical number of subjects taking vitamin E died during the course of the trial compared to patients taking placebo. Based on this single study, and the theoretical benefits of anti-oxidants in preventing AD and cognitive decline as well as aging in general, a large number of AD and MCI subjects are currently prescribed vitamin E, or obtain it themselves from pharmacies.

The evidence for a benefit from vitamin E in preventing or delaying AD derives from a set of epidemiologic studies.[61-63] In contrast to this is new evidence from the large "Memory Impairment Study," in which individuals with MCI were recruited and randomized into a vitamin E therapy arm, a donepezil therapy arm, or a placebo arm. The crucial primary endpoint was the number of subjects classified as progressing to dementia at the end of three years. This study assessed the effects of five daily capsules of vitamin E (2000 IU) and

found no overall benefit in the vitamin E group in terms of prevention of progression to AD at the end of three years.[64]

Furthermore, a recent meta-analysis raised questions about the safety of vitamin E when given at such a high dose. Miller et al examined the number of deaths in 19 clinical trials of vitamin E, including a total of 136,000 subjects.[65] None of the individual studies showed an increase in risk of death for subjects taking vitamin E alone. However, when the studies were arranged by dose of vitamin E (above or below the 400 IU/day median dose), it appeared that individuals taking low to moderate doses of vitamin E had a very slight protection against death while those taking high-dose vitamin E were at a very slightly higher risk of death. There are, however, numerous methodological weaknesses in this study.

Despite the meta-analysis, the risk of vitamin E also appears minimal. Might a single 400 IU vitamin E tablet be beneficially and safely prescribed for an MCI individual? They receive this in my own clinic, albeit with some hesitation. The recent Canadian Consensus Conference concluded that there is currently fair evidence to recommend against the use of vitamin E therapy in MCI.

## Can Cholinesterase Inhibitors Slow and Prevent AD?

The "Memory Impairment Study" described earlier was an important three-year trial co-sponsored by the National Institute of Aging (NIA), the Alzheimer Disease Cooperative Study group (ADCS), and Pfizer. In this study, individuals with MCI were recruited and randomized into a vitamin E arm (2000 IU daily), a donepezil arm (10 mg daily), or a placebo arm. The crucial primary endpoint was the number of subjects classified as progressing to dementia at the end of three years. The result was negative—no significant differences between the three groups were found at three years.[64] This disappointing result seems to put to rest the possibility of CIs as effective therapies to prevent AD, but there are sub-analyses that seem still to offer promise. For instance, it is clear that the group of individuals taking donepezil performed better than the others over the first 18 months, in terms of neuropsychological measures and global outcomes. It is also clear that the majority of individuals progressing to AD had an Apo-E4 allele, and if the analysis is restricted only to those individuals, there were indeed less "conversions to dementia" with donepezil at the end of three years. Currently, debate rages on whether this "negative study" might be reinterpreted as a positive result for a particular subgroup of patients. There are also the usual methodological concerns (heterogeneity of patients, weak outcome measure) that make it hard to achieve significant results even with large numbers of subjects.

***There are nine kinds of potential prevention therapies that cannot currently be recommended. These each could theoretically delay or prevent progression to AD from the MCI state, but have failed to reach sufficient strength of evidence to be recommended.***

The other main CIs are also being assessed for their potential to slow progression to AD. The galantamine trial was a two-year study focusing on amnestic MCI patients with memory below a cutoff on paragraph recall. There was no difference in the primary analysis of conversion from amnestic MCI to AD. There did appear to be a reduced rate of whole-brain atrophy in the patients treated with galantamine.[66] However, therapy with this medication was associated with a small but statistically significant increased risk of dying. The sponsoring company discontinued the trial and has not recommended therapy for MCI with galantamine.[67]

The bottom line is that from the current evidence, if there is a benefit of CIs in slowing progression to AD, it appears to be transient as well as limited.[68]

## Therapy for Vascular Risk Factors

It is clear that vascular damage impacts on the occurrence of AD and mixed dementia. Risks for vascular disease (diabetes, hypertension, smoking, obesity, hyperlipidemia) are being proven to be risk factors for the development of dementia. In the Rotterdam Study in the Netherlands, individuals with diabetes had nearly double the risk of dementia.[69] Presumably, the microvascular damage from diabetes is the culprit, although it is possible that higher-than-normal levels of glucose in the blood might be toxic. The Framingham Heart Study demonstrated an impact of hypertension on cognition six years later.[70] The Cardiovascular Health Study showed that cognitive decline occurred even without frank stroke in individuals with vascular risk factors.[71]

These data give us additional approaches to therapy of MCI, namely aggressively treating vascular risk factors. Several randomized controlled studies of antihypertensives after stroke have shown a clear effect in reducing the subsequent incidence of dementia.[72-74] One clinical trial evaluated the role of hypertension treatment in individuals with mild cognitive deficits broadly defined as a Mini-Mental Status Examination score between 20 and 28.[75] Patients with the best response to treatment, in terms of reduction of their diastolic blood pressure, significantly improved on two cognitive tests.

Note that this therapy is unproven in the sense that no one has yet mounted a long-term study proving that intervention at the MCI stage will be effective in reducing or preventing dementia or AD. However, treating these risks makes sense in its own right—a patient with uncontrolled hypertension should be treated anytime. Thus, in recommendations to family physicians, those working to prevent AD are now giving strong advice to "do what you already do"—namely, aggressively treat any risk factors for vascular disease, in a patient with MCI. The risk of dementia thus represents an additional reason to treat the patient.

***Vitamin E, an anti-oxidant, has had a roller-coaster profile as a medication to prevent dementia, and this highlights the challenges and difficulties in deriving preventive therapies for a chronic disease like AD.***

## The MCI Diet

Given the factors identified above, it is interesting to note that dietary interventions are possible in the treatment of MCI or prevention of dementia. A healthy diet helps prevent hypertension (via reduced saturated fats and sodium), prediabetes (reduce sweets and caloric intake and consume more fibre), and stroke (dietary change to reduce cholesterol). Obesity is to be avoided by dietary limitation and exercise. One study reported a higher risk of AD in seniors who ate more saturated and trans fat and less unsaturated fat, but another study did not find the same link.[76]

Analysis of the Framingham study produced the somewhat surprising result that higher homocysteine levels were associated with increased risk of sporadic AD.[77] It is known that increased serum homocysteine is associated with histopathologic evidence of vascular endothelial injury, vascular smooth muscle proliferation, and progressive arterial stenosis.[78] The factors in homocysteine levels are well known—vitamin supplements (folate, B6, B12) lower the levels, while caffeine, smoking, and lack of exercise increase levels. Current management of elevated homocysteine has been to increase folate in the diet or treat with supplements when increased homocysteine was greater than 15 µmol/L. Simple treatment with folate (3 mg daily), B6 (25 mg daily), and B12 (250 to 500 µg daily) keeps the homocysteine level low. Homocysteine levels (high or even normal) can in theory be reduced by a good intake of folic acid, B6, and B12 found in green leafy vegetables. Several multi-vitamins a day will also supply these amounts.

Omega fatty acids, particularly DHA (docosahexaenoic acid), can be obtained by eating cold-water fatty fish such as salmon, sardines, mackerel, and bluefish. There is evidence that individuals whose diets are high in omega-3 fatty acids, especially DHA, have a 50% reduction in their risk of developing dementia.[79,80] Some doctors are now recommending that MCI patients eat such fish (or take two 200 mg DHA capsules) three times weekly.[79,80] This therapy also did not receive recommendation from the Canadian Consensus Conference on dementia, however. About 180 mg of DHA daily intake is suggested and this amount can be achieved by eating the fish previously mentioned about three times per week. Thus, there is a theoretical basis for considerable dietary manipulation in MCI, none yet supported by RCTs.

## Current Treatment of MCI

Given the lack of clear prognostic markers, heterogeneity in the natural history of MCI individuals, and lack of proven therapies to prevent decline, the management of MCI patients remains largely non-specific. The strongest evidence supports suggestions to "maintain a healthy lifestyle" with adequate exercise, avoidance of obesity, mental and physical stimulation, control of stress, treatment of medical illnesses and depression, and control of vascular risk factors such as diabetes, hypetension, and hypercholesterolemia.

Currently we lack proven pharmacologic approaches to prevent cognitive decline or progression from MCI to dementia. It makes good sense to aggressively treat vascular risk factors in MCI individuals using lifestyle interventions, diet and medications when necessary. Pharma-cologic treatment of depr-ession is also indicated. Drugs with known anticholinergic activity, as well as sleeping pills and sedatives, should be avoided.

Physicians should inform patients that there is no current specific treatment for MCI sufficiently substantiated to have obtained government approval. Treating MCI individuals (or the healthy elderly) in order to prevent subsequent AD using CIs, anti-inflammatories, estrogen, statins, various antioxidants or even vitamin E, represents prescription beyond proven therapies. It is advisable to refer the eager MCI patient to a research clinic where RCTs of these and other preventive medications are currently underway.

***Thus, in recommendations to family physicians, those working to prevent AD are now giving strong advice to "do what you already do"—namely, aggressively treat any risk factors for vascular disease, in a patient with MCI.***

The Memory Impairment Study raises significant therapeutic issues. Since there was a delay in progression to AD in MCI individuals with a positive ApoE4 perhaps "a discussion of therapy" with donepezil is warranted. But what discussion? Should MCI patients be offered genetic testing with ApoE prior to a therapy decision? Should donepezil be offered with the hope that the symptomatic benefit will make up for our uncertainty regarding its long-term prevention role? Should its role in MCI (and the role of CIs in general) be downplayed as a major part of our therapeutic armamentarium, rather than using them up at the MCI stage?

In our own clinic, we have exploited the dietary possibilities noted above as a way to maximize the potential beneficial effects of anti-oxidants and omega fatty acids, and to control homocysteine levels. Our patients generally are encouraged to take one or two multivitamins daily, which deliver adequate doses of vitamin E (400 IU), along with B6 and folate supplementation. This is really all they are offered at the current time. The rest remains in the realm of current research and future possibilities.

References:
1. Petersen RC, Mild cognitive impairment as a diagnostic entity. J Intern Med 2004; 256(3):183-94.
2. Chertkow H, Mild Cognitive Impairment. Curr Opin Neurol 2002; 15(4):401-7.
3. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment—beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med 2004; 256(3):240-6.
4. Tombaugh TN, McIntyre NJ. The Mini-mental state examination: A comprehensive review. J Am Geriatr Soc 1992; 40:922-35.
5. Petersen RC and JC Morris, Mild cognitive impairment as a clinical entity and treatment target. Arch Neurol 2005; 62(7):1160-3; discussion 1167.
6. Davis HS, Rockwood K. Conceptual-ization of mild cognitive impairment: a review. Int J Geriatr Psychiatry 2004; 19(4):313-9.
7. Luis CA, Lowenstein DA, Acevedo A, et al. Mild cognitive impairment: directions for future research. Neurology 2003; 61(4):438-44.
8. Gauthier S, Reisberg B, Zaudig M et al. Mild cognitive impairment. The Lancet 2006; 367:1262-70.
9. Morris JC, Price AL. Pathologic correlates of nondemented aging, mild cognitive impairment, and early-stage Alzheimer's disease. J Mol Neurosci 2001; 17(2):101-18.
10. Morris JC, Storandt M, Miller JP, et al. Mild cognitive impairment represents early-stage Alzheimer disease. Arch Neurol 2001; 58(3):397-405.
11. Ritchie K, Touchon J. Mild cognitive impairment: conceptual basis and current nosological status. Lancet 2000; 355:225-8.
12. Bocti C, Whitehead V, Fellow L, et al. Characteristics of patients with Mild Cognitive Impairment who do not progress to dementia. 57th Annual Meeting American Academy of Neurology 2005; Miami Beach, Florida.
13. Fisk JD, Rockwood K. Outcomes of incident mild cognitive impairment in relation to case definition. J Neurol Neuro-surg Psychiatry 2005; 76(8):1175-7.
14. Kramer AF, Bherer L, Colcombe SJ, et al. Environmental influences on cognitive and brain plasticity during aging. J Gerontol A Biol Sci Med Sci 2004; 59(9):M940-57.
15. Lindstrom HA, Pritsch T, Petot G, et al. The relationships between television viewing in midlife and the development of Alzheimer's disease in a case-control study. Brain Cogn 2005; 58(2):157-65.
16. Wilson RS, Mendes De Leon CF, Barnes LL, et al. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. JAMA 2002; 287(6):742-8.
17. Verhaeghen P, Marcoen A, Goossens L. Improving memory performance in the aged through mnemonic training: a meta-analytic study. Psychol Aging 1992; 7(2):242-51.
18. Ball K, Berch DB, Helmers KF, et al. Effects of cognitive training interventions with older adults: a randomized controlled trial. JAMA 2002; 288(18):2271-81.
19. Gunther VK, Schafer P, Holzner BJ, et al. Long-term improvements in cognitive performance through computer-assisted cognitive training: a pilot study in a residential home for older people. Aging Ment Health 2003; 7(3):200-6.
20. Olazaran J, Muniz R, Reisberb B, et al. Benefits of cognitive-motor intervention in MCI and mild to moderate Alzheimer disease. Neurology 2004; 63(12):2348-53.
21. Belleville S, et al. Improvement of episodic memory in persons with Mild Cognitive Impairment and healthy older adults: Evidence from a cognitive intervention program. (in press). Dement Geriatr Cogn Disord, 2006.
22. Rapp S, Brenes G, Marsh AP. Memory enhancement training for older adults with mild cognitive impairment: a preliminary study. Aging Ment Health 2002; 6(1):5-11.
23. Lytle ME, Vander Bilt J, Pandav RS, et al. Exercise level and cognitive decline: the MoVIES project. Alzheimer Dis Assoc Disord 2004; 18(2):57-64.
24. Laurin D, Verreault R, Lindsay J, et al. Physical activity and risk of cognitive impairment and dementia in elderly persons. Arch Neurol 2001; 58(3):498-504.
25. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Sci 2003; 14(2):125-30.
26. Heyn P, Abreu BC, Ottenbacher KJ. The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. Arch Phys Med Rehabil 2004; 85(10):1694-704.
27. Chertkow H, Nasreddinne Z, Massoud F, et al. Mild Cognitive Impairment—Recommendations on Diagnosis and Therapy from the Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia. BMC Geriatrics, submitted 2006.
28. Lupien SJ, Nair NP, Briere S, et al. Increased cortisol levels and impaired cognition in human aging: implication for depression and dementia in later life. Rev Neurosci 1999; 10(2):117-39.
29. Sapolsky R, Krey L, McEwen B. The neuroendocrinology of stress and aging: the glucocorticoid cascadde hypothesis. Endocrinol Review 1986; 7:284-301.
30. Issa AM, Rowe W, Gauthier S, et al. Hypothalamic-pituitary-adrenal activity in aged, cognitively impaired and cognitively unimpaired rats. J Neurosci 1990; 10(10):3247-54.
31. Wilson RS, Barnes LL, Bennett DA, et al. Proneness to psychological distress is associated with risk of Alzheimer's disease. Neurology 2003; 61(11):1479-85.
32. Bliwise DL. Is sleep apnea a cause of reversible dementia in old age? JAGS 1996; 44:1407-9.
33. Boeve BF, Silver MH, Ferman TJ, et al. Association of REM sleep behavior disorder and neurodegenerative disease may reflect an underlying synucleinopathy. Mov Disord 2001; 16(4):622-30.
34. Riemann D, Hohagen F, Krieger S, et al. Cholinergic neurotransmission, REM sleep and depression. J Psychosom Res 1994; 38(Suppl 1):15-25.
35. Adler G, Bramesfeld A, Jajcevic A, Mild cognitive impairment in old-age depression is associated with increased EEG slow-wave power. Neuropsychobiology 1999; 40(4): 218-22.
36. Alexopoulos GS, Heterogeneity and comorbidity in dementia-depression syndromes [editorial]. Int J Geriatr Psychiatry 1991; 6(3): 125-7.
37. Coen RF, Kirby M, Swanwick GR, et al. Distinguishing between patients with depression or very mild Alzheimer's disease using the delayed-word-recall test. Dement Geriatr Cogn Disord 1997; 8(4): 244-7.
38. Reischies FM, Neu P. Comorbidity of mild cognitive disorder and depression—a neuropsychological analysis. Eur Arch Psychiatry Clin Neurosci 2000; 250(4):186-93.
39. Alexopoulos G, Schultz SK, Lebowitz BD, et al. The course of geriatric depression with "reversible dementia": a controlled study. Am J Psychiatry 1993; 150(11):1693-9.
40. Fratiglioni L, et al. Influence of social network on occurrence of dementia: a community-based longitudinal study. Lancet 2000; 355(9212): 1315-9.
41. Ihl R. The impact of drugs against dementia on cognition in aging and mild cognitive impairment. Pharmacopsychiatry 2003; 36 Suppl 1:S38-43.
42. Lanctot KL, Herrman N, Yau KK, et al. Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: a meta-analysis. CMAJ 2003; 169(6):557-64.
43. Patterson C, Gauthier S, Bergman H, et al. The recognition, assessment and management of dementing disorders: conclusions from the Canadian Consensus Conference on Dementia. CMAJ1999; 160(suppl 12):S1-S15.
44. Reisberg B, Doody R, Stoffler A, et al., Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med, 2003; 348(14):1333-41.
45. Salloway S, Ferris S, Kluger A, et al. Efficacy of donepezil in mild cognitive impairment: a randomized placebo-controlled trial. Neurology 2004; 63(4): 651-7.
46. McDaniel MA, Maier SF, Einstein GO. "Brain-specific" nutrients: a memory cure? Nutrition 2003; 19(11-12):957-75.
47. Le Bars PL, Katz MM, Berman N, et al. A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia. North American EGb Study Group. JAMA 1997; 278(16):1327-32.
48. Van Dongen M, Van Rossum E, Kessels A, et al. Ginkgo for elderly people with dementia and age-associated memory impairment: a randomized clinical trial. J Clin Epidemiol 2003; 56(4):367-76.
49. Riedel WJ, Jolles J. Cognition enhancers in age-related cognitive decline. Drug and Aging 1996; 8(4):245-74.
50. Crook TH, Ferris SH, Alvarez XA, et al. Effects of phosphatidylserine in age-associated memory impairment. Neurology 1991; 41(5):644-9.

51. Israel L, Melac M, Milinkevitch D, et al. Drug therapy and memory training programs: a double-blind randomized trial of general practice patients with age-associated memory impairment. Int Psychogeriatr 1994; 6(2):155-70.
52. Tully T, Bourtchouladze R, Scott R, et al. Targeting the CREB pathway for memory enhancers. Nat Rev Drug Discov 2003; 2(4):267-77.
53. Lynch G. Memory enhancement: the search for mechanism-based drugs. Nat Neurosci, 2002. 5 Suppl: 1035-8.
54. Farah MJ, Illes J, Cook Deegan R, et al. Neurocognitive enhancement: what can we do and what should we do? Nat Rev Neurosci 2004; 5(5):421-5.
55. Pepeu G. Overview and perspective on the therapy of Alzheimer's disease from a preclinical viewpoint. Progress in Neuro-Psychopharmacology & Biological Psychiatry 2001; 25(1):193-209.
56. Danysz W. CX-516 Cortex pharmaceuticals. Curr Opin Investig Drugs 2002; 3(7):1081-8.
57. Squire LR, Kandel ER, Memory: From Mind to Molecules. New York(1999): W.H. Freeman & Co.
58. Markesbery WR. Oxidative stress hypothesis in Alzheimer's disease. Free Radic Biol Med 1997; 23(1):134-47.
59. Perry G, Nunomura A, Hirai K, et al. Is oxidative damage the fundamental pathogenic mechanism of Alzheimer's and other neurodegenerative diseases? Free Radic Biol Med 2002; 33(11):1475-9.
60. Sano M, Ernesto C, Thomas RG, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. N Engl J Med 1997; 336(17):1216-22.
61. Morris MC, Evans DA, Brenias JL, et al. Vitamin E and cognitive decline in older persons. Arch Neurol 2002; 59(7):1125-32.
62. Engelhart MJ, Geerlings MI, Ruittenberg A, et al. Dietary intake of antioxidants and risk of Alzheimer disease. JAMA 2002; 287(24):3223-9.
63. Fotuhi M, Hayden KM, Zandi P, et al. Use of NSAIDs and antioxidant supplements in combination reduces the rate of cognitive decline. the cache county study. Alzheimer's & Dementia, the journal of the Alzheimer's association 2005; 1:S97-8.
64. Petersen RC,Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 2005; 352(23):2379-88.
65. Miller ER, Pastor-Barriuso R, Dalal D, et al. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med 2005;142(1):37-46.
66. Scheltens P, Fox NC, Barkhof F, et al. Effect of galantamine treatment on brain atrophy as assessed by MRI in patients with mild cognitive impairment. Neurobiol Aging 2004; 25(suppl.2):S270-1.
67. Advisory, H.C.P., Health Canada Endorsed Important Safety Information on Reminyl (Galantamine). January 2005. available at: *http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_advisories_public_e.html.*
68. Blacker D, Mild cognitive impairment-no benefit from vitamin E, little from donepezil. N Engl J Med, 2005. 352(23):2439-41.
69. Ott A, Van Harskamp F, Stolk RP, et al. Diabetes mellitus and the risk of dementia: The Rotterdam Study. Neurology 1999; 53(9):1937-42.
70. Elias MF, Elias PK, Sullivan LM, et al. Lower cognitive function in the presence of obesity and hypertension: the Framingham heart study. Int J Obes Relat Metab Disord 2003; 27(2):260-8.
71. Elkins JS, O'Meara ES, Longstreth WT, et al. Stroke risk factors and loss of high cognitive function. Neurology 2004; 63(5): 793-9.
72. Forette F, Seux ML, Staessens JA, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet 1998; 352(9137):1347-51.
73. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002; 360(9346):1623-30.
74. Tzourio C, Dufouil C, Ducimetiere P, et al. Cognitive decline in individuals with high blood pressure: a longitudinal study in the elderly. EVA Study Group. Epidemiology of Vascular Aging. Neurology 1999; 53(9):1948-52.
75. Starr JM, Deary IJ. The effects of antihypertensive treatment on cognitive function: results from the HOPE study. J Am Geriatr Soc 1996; 44:411-5.
76. Morris MC, Evans DA, Brenias JL, et al. Dietary fats and the risk of incident Alzheimer disease. Arch Neurol 2003; 60(2):194-200.
77. Seshadri S, Beiser A, Selhub J, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med, 2002. 346(7):476-83.
78. Miller JW, Green R, Mungus DM, et al. Homocysteine, vitamin B6, and vascular disease in AD patients. Neurology 2002; 58(10): 1471-5.
79. Engelhart MJ, Geerlings MI, Ruitenberg A, et al. Diet and risk of dementia: Does fat matter? The Rotterdam Study. Neurology 2002; 59(12):1915-21.
80. Kalmijn S, Feskens EJ, Launer LJ, et al. Polyunsaturated fatty acids, antioxidants, and cognitive function in very old men. Am J Epidemiol, 1997. 145(1):33-41.
81. Perrig WJ, Perrig P, Stahelin HB. The relation between antioxidants and memory performance in the old and very old. J Am Geriatr Soc 1997; 45(6):718-24.
82. Etminan M, Gill S, Samii A. Effect of non-steroidal anti-inflammatory drugs on risk of Alzheimer's disease: systematic review and meta-analysis of observational studies. BMJ 2003; 327(7407):128-31.
83. Aisen PS, Schafer KA, Grundman M, et al. Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial. JAMA 2003; 289(21): 2819-26.
84. Yaffe K, Sawaya G, Lieberburg I, et al. Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. JAMA 1998; 279(9): 688-95.
85. Maki PM, Resnick SM. Effects of estrogen on patterns of brain activity at rest and during cognitive activity: a review of neuroimaging studies. Neuroimage 2001; 14(4):789-801.
86. Yaffe K, Krueger K, Cummings SR, et al. Effect of raloxifene on prevention of dementia and cognitive impairment in older women: the Multiple Outcomes of Raloxifene Evaluation (MORE) randomized trial. Am J Psychiatry 2005; 162(4): 683-90.
87. Shumaker SA, Espeland MA, Rapp SR, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA 2004; 291(24):2947-58.
88. Rapp SR, Espeland MA, Shumaker SA, et al. Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 2003; 289(20):2663-72.
89. Kang JH, Weuve J, Grodstein F. Postmenopausal hormone therapy and risk of cognitive decline in community-dwelling aging women. Neurology 2004; 63(1):101-7.
90. Jick H, Zornberg GL, Jick SS, et al. Statins and the risk of dementia. Lancet 2000; 356(9242):1627-31.
91. Wolozin B, Kellman W, Rousseau P, et al. Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors. Arch Neurol 2000; 57(10):1439-43.
92. Sparks DL, Sabbagh MN, Connor PJ, et al. Atorvastatin for the treatment of mild to moderate Alzheimer disease: preliminary results. Arch Neurol 2005; 62(5):753-7.
93. Schenk D. Amyloid-beta immunotherapy for Alzheimer's disease: the end of the beginning. Nat Rev Neurosci 2002; 3(10):824-8.
94. Schenk D, Barbour R, Dunn W, et al. Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse [see comments]. Nature 1999; 400(6740):173-7.

# ABSTRACTS

Fischer P. **Conversion of subtypes of mild cognitive impairment within 30 months in the Vita* study. Presented at the 9th International Geneva/Springfield Symposium on Advances in Alzheimer Therapy, April 19-22, 2006, Geneva, Switzerland.**

## METHODS

This study investigated a community-based age cohort of elderly born between May 1925, and June 1926. Each individual, aged 75 years old, underwent neuropsychological testing at the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), (which tests verbal- and non-verbal memory, naming, fluency and constructional praxis), and the Trail Making Test B (which tests executive function). A total of 440 (72.7%) subjects performed normally on all six tested cognitive dimensions. A total of 141 subjects (23.3%) showed cognitive impairment without dementia after one or more cognitive tests (1.5 standard deviation paradigm). These subjects were assigned to four subtypes of mild cognitive impairment (MCI): amnestic MCI single type, $n$ = 21; amnestic MCI multiple type, $n$ = 27; non-amnestic MCI single type, $n$ = 69; and non-amnestic MCI multiple type, $n$ = 24. After a period of 30 months (at the age of 78 years), patients are examined for AD, applying the NINCDS-ADRDA criteria.

## RESULTS

Of the 390 cognitively healthy subjects at baseline, 49 (13%) converted to possible/probable AD, 43 (11%) to MCI, and 35 (9%) died. Of the 39 subjects with amnestic MCI at baseline, 19 (49%) converted to AD, 10 (26%) were classified again with MCI, and 6 (15%) converted to cognitive health (2 subjects died, 1 non-demented subject was unclassifiable, 1 subject converted to vascular dementia without AD). Of 82 non-amnestic MCI subjects at baseline, 20 (24%) converted to cognitive health, 30 (37%) were again diagnosed with MCI at follow-up, 22 (27%) converted to AD, and 8 (10%) died (1 converted to vascular dementia without AD). It was concluded that amnestic MCI and, to a lesser degree, non-amnestic MCI, significantly predicted conversion to AD between the ages of 75 and 78 years. A diagnosis of MCI at 75 years old did not increase mortality for the next 30 months.

Deschaintre Y, Capele C, Richard F, et al. **Vascular risk factors treatment slows cognitive decline. Presented at the 9th International Geneva/Springfield Symposium on Advances in Alzheimer Therapy, April 19-22, 2006, Geneva, Switzerland.**

## METHODS

This study evaluated whether treatment for vascular risk factors slows cognitive decline in Alzheimer's disease (AD), AD with vascular component (ADVC) and vascular dementia (VaD). The study comprised of patients who attended a memory clinic for the first time in 1997, with at least two mini-mental status examinations (MMSE) more than six months apart and with a final diagnosis of AD, ADVC or VaD. Mention of high blood pressure, diabetes, dyslipidemia or atherosclerotic vascular disease was sought at their first complete evaluation. Vascular risk factors were considered treated if they received, respectively, an antihypertensive, an oral antihyperglycemic or insulin, a statin or a fibrate, an antiplatelet or an anticoagulant.

## RESULTS

Within the 142 cases included, 125 (88%) had at least one vascular risk factor; 59 (47.2%) were treated and 66 (52.8%) were not treated or only partially treated. Dyslipidemia was the vascular risk factor least likely to be treated (25% treated). The treated and untreated groups were similar in age (72.3 years old), gender (55.2% women), education level (72% low level), time since symptoms first appeared (4.5 years), diagnosis (54.4% AD, 20.8% ADVC and 24.8% VaD), acetylcholinesterase inhibitor exposition (61.6%) and follow-up time (4.1 years). MMSE mean annual decline (±standard deviation) was respectively 1.47±2.59 and 2.80±4.03 points ($p$ = 0.029, bilateral student t-test). It was concluded that treatment for vascular risk factors is associated with a slower decline of MMSE.

Freund-Levi Y, Eriksdotter-Jonhagen M, Cederholm T, et al. **Omega-3 fatty acid treatment of 174 patients with mild to moderate Alzheimer disease: a randomised double-blind trial. Presented at the 9th International Geneva/Springfield Symposium on Advances in Alzheimer Therapy, April 19-22, 2006, Geneva, Switzerland.**

## METHODS

This was a double-blind, placebo-controlled clinical trial, where 204 Alzheimer disease (AD) patients (74±9 years) with acetylcholine esterase inhibitor treatment and a mini-mental status examination (MMSE ) score > 15 points were randomized to daily intake of omega-3 fatty acids (Ω3 FA), docosahexaenoic acid (DHA) 1.7g and eicosapentaenoic acid (EPA) 0.6g, or placebo for six months. After this time, patients received the Ω3 FA for six additional months. The primary outcome was global function (assessed with the Clinical Dementia Rating (CDR) scale), safety, tolerability and blood pressure.

## RESULTS

A total of 174 patients fulfilled the trial. At baseline, mean CDR, MMSE, and ADAS-cog values in all patients were similar. At six months the decline in cognitive functions, as assessed by the two latter scales, did not differ between the groups. However, in a subgroup ($n$ = 32) with very mild cognitive dysfunction (*i.e.,* MMSE > 27 points), a significant reduction in MMSE decline rate was observed ($p < 0.05$) in the Ω3 group compared to the placebo group. A similar arrest in decline rate was observed in this placebo subgroup when receiving Ω3 FA between 6 and 12 months. Safety and tolerability was excellent. It was concluded that Ω3 FA given to moderate AD patients did not delay the rate of cognitive decline according to MMSE or ADAS-cog scales. However, positive effects were observed in a small group of patients with very mild AD (MMSE > 27).

Korczyn AD,Verchovsky R, Vakhapova V, et al. **Apparent efficacy and reasons of discontinuation of cholinesterase inhibitors in Alzheimer disease. Presented at the 9th International Geneva/Springfield Symposium on Advances in Alzheimer Therapy, April 19-22, 2006, Geneva, Switzerland.**

## METHODS

This study's objective was to determine the apparent efficacy of two cholinesterase inhibitors, rivastigmine and donepezil, through the rate and reasons for cessation of treatment. A retrospective study design was used, including medical record reviews and telephone call to the patients and caregivers as needed.

## RESULTS

Data were collected on the severity of disease, type and duration of treatment and reasons for discontinuation in 125 patients (66 females) who were treated in an out-patient clinic between 2000 and 2004. Of the 66 patients who had started treatment on donepezil, 30 discontinued (45%), 21 due to apparent lack of efficacy, 2 due to side effects and 7 due to other reasons. The mean duration of treatment was 35.7±20.3 months, median 34. The results of the MMSE at onset of the treatment were mean 20±4.3, median 22, and at discontinuation were mean 13±4.9, median 11. Rivastigmine was given to 59 patients, of whom 33 discontinued (56%) treatment. Of those, 14 discontinued due to apparent lack of efficacy, 11 due to side effects and 8 due to other reasons. The mean duration of treatment was 27.7±18.8 months, median 26. The results of the MMSE at onset of the treatment were mean 21±3.5, median 23, and at discontinuation mean 17±4.7, median 16. A two-tailed t-test for differences of duration of treatment between the two groups favored donepezil ($p$ = 0.041). It was concluded that patients seem to be maintained longer on donepezil than on rivastigmine. Apparent lack of efficacy was the main reason for the discontinuation of both agents. The efficacy of both treatments seemed similar.

# Case Study: Margaret

*by Paul Coolican, MD*
*Dr. Coolican is a Family Physician at the St. Lawrence Medical Clinic in Morrisburg, Ontario and on Active Staff at the Winchester District Memorial Hospital in Winchester, Ontario.*

**Case Study**

**Medical History**

- **T1NO breast cancer, diagnosed at age 60 years; treated with modified radical mastectomy and prescribed tamoxifen for 5 years**
- **Mild hypertension, treated with hydrochlorthiazide**

**Social History**

- **High-school education and 1 year university**
- **Widowed with two children at age 31 years; remarried at age 54 years; 5 grandchildren**
- **Non smoker; alcohol average 3 drinks per week**

**Family History**

- **7 siblings, 2nd youngest**
- **Parents died in their 80s, "old age"**
- **3 siblings deceased: 1 MI at age 68 years, 1 breast cancer at age 70 years, 1 pneumonia at age 81 years (was in nursing home)**

## Case Background

Margaret is a 72-year-old patient whom you have treated for over 15 years. She visits you with her husband which is unusual. In the past she has always come to see you on her own, even after developing breast cancer 12 years ago. She is uncomfortable seeing you in his presence and after a few pauses he states that she is not herself, that she has lost interest in her friends and even her family. He says she is irritable when he tries to persuade her to go out or visit. She is not sleeping well and he wonders if sleep medication might allow her to sleep better and make her feel better about life.

## Medical Examination

Margaret's physical examination is essentially unchanged. She scores 12/30 on a Geriatric Scale Questionnaire which indicates mild depression. A mini-mental status examination (MMSE) is administered and she scores 25/30, losing 2 points in short-term recall, 2 in spelling "world" backwards, and 1 in orientation (mistaking seasons). A clock drawing at 10 after 11 shows abnormal crowding of the numbers in the 9 to 12 quadrant but the arm placement is correct.

She undergoes further medical testing (all negative) and is referred to a memory disorder clinic. A tentative diagnosis of mild dementia with depression is made.

## Case Discussion

The distinction between and treatment of dementia and depression is gaining importance as evidence mounts to suggest that early treatment of these conditions reduces the risk and degree of future impairment. Recent studies suggest that individuals suffering from depression are more likely to develop mild cognitive impairment (MCI). Furthermore, it is suggested that individuals suffering from depression with MCI are at increased risk to develop dementia and that onset of dementia may be shorter in depressed individuals. Early and appropriate treatment may help to slow any decline in cognitive function and maintain independent function.

Screening for dementia and Alzheimer's disease in the family physician office usually relies upon the MMSE. In Margaret's case, her education level and age suggest that her MMSE score should be > 28/30. The MMSE is thought to be effective in distinguishing mild AD from depression but has difficulty distinguishing MCI from depression. Sometimes however, it is valuable to corroborate your findings by using the more comprehensive testing available at such facilities as a memory disorder clinic.

For this particular patient, a history of breast cancer mandated further medical testing that included CT head, ALP, Bone Scan as well as the more usual CBC, TSH, B12, Calcium, electrolytes and glucose. This was all normal and she was referred to a memory disorder clinic.

References:

1. Barnes DE, Alexopoulos GS, Lopez OL, et al. Depressive symptoms, vascular disease, and mild cognitive impairment: findings from the Cardiovascular Health Study. Arch Gen Psychiatry 2006; 63(3):273-9.
2. Modrego PJ, Ferrandez J. Depression in patients with mild cognitive impairment increases the risk of developing dementia of Alzheimer type: a prospective cohort study. Archives Neurology 2004; 61(8):1290-3.
3. Benson AD, Slavin MJ, Tran TT, et al. Screening for Early Alzheimer's Disease: Is There Still a Role for the Mini-Mental State Examination? Care Companion J Clin Psychiatry 2005; 7(2): 62–9.

## Case Discussion

The diagnosis and management of patients with dementia is complex. Symptoms are often not clear-cut or clearly manageable. **The Canadian Review of Alzheimer's Disease and Other Dementias** invites you, the readers, to send your comments on Margaret's case. A selection of your responses will be printed in the next issue.

Send your comments to: *alzheimer@sta.ca* or by fax: 1-888-695-8554

PERSPECTIVES

# Personal Revelations, Experiences and Reflections of an AD Caregiver

Roberta Bedard is a caregiver for her husband who has Alzheimer's disease (AD). She has written many humorous and touching vignettes about her personal experiences in dealing with the development of the disease and has graciously agreed to feature these vignettes as a series in *The Canadian Review of Alzheimer's Disease and Other Dementias*. Roberta's writings enable readers to share in her journey with AD caregiving, provide valuable insight on the human aspect of disease and stimulate contemplation on the deeper meanings of life and love.

***In this feature...***

In "He's Gone," Roberta writes about her final days with her husband and the pain of letting him go. His brain has forgotten how to swallow. Because he has refused life-prolonging measures, for seven days, from his bedside, Roberta watches him slip away.

## CHAPTER 9

*by Roberta Bedard*

*He's gone. He's gone. He's Gone!!!* I can find no words to more clearly express what I feel. He's gone! This enormity precludes my ability to form a coherent sentence that will say what I am feeling. It will be weeks, months maybe, before I can pull myself together enough to write the final chapter in the saga of the journey Ray and I have taken through the world of AD.

*Later*. I am a widow. How did this happen? Oh, I know the "facts." Ray caught pneumonia. He went to acute care. With hydration and antibiotics his strong body and heart recovered. But in the meantime, his brain forgot how to swallow. He could not be maintained on hydration alone, and his Personal Directive prohibited intrusive measures to prolong his life. His doctor and I made the decision that we were morally, ethically and legally bound to make. Remove the hydration intubator. Let him go. Keep him comfortable and pain-free. Let him go.

Well, I thought I had cried before. I thought I understood tears. He lingered for seven days. It finally dawned on me that he was holding on because, on some level, he was worried about me. Until he became non-responsive, he would weakly clasp my hand when I told him I would be all right, that it was okay for him to slip away. It wasn't until I asked everyone who came into the room to tell him that they would look after me that I felt his body relax.

Except for going home to feed the cat and to bathe, I was at his bedside day and night. He had asked me to be with him, alone, in his final moments and I was determined to keep that promise. Being with him gave me one moment that will comfort me (if comfort ever becomes possible) until my own last days. We connected. His eyes met mine and there was nothing in the way. No Alzheimer's. No fear. Just a pure meeting of souls. It lasted only a second. But it was real. Had I not been there at that precise moment, I would have missed it.

My unscientific and unsupported opinion is that this was similar to the surge of energy anorexics feel just before their bodies give up. A last desperate marshalling of forces. I don't expect anyone to agree with me. But I was there. I felt it. I know it to be true that we connected.

Then he slipped away into non-responsiveness. The staff kept him clean, changed his position every two hours, and gave him morphine every three hours so he would not feel any pain in his stomach or anywhere else (though I had to be forceful with the nurse who kept trying to give him half-doses—Why?). My position was that he had no way to communicate whether or not he was feeling pain. I was not prepared to risk his feeling *any* discomfort.

I sat in the recliner. Sometimes I dashed to the cafeteria and back. Sometimes staff brought me food.

He became tinier. Then his life force left him. I had heard that sometimes the dying wait until they are alone to leave us. I think in his final moment, Ray did that. I was beside him, holding his hand, and drifted into a light sleep. I don't know for how long. When I awoke, he was gone.

I have seen films where those around a death bed look for a pulse, question whether the death really occurred. I don't understand this. The difference is obvious. Before he died, non-responsive though he was, I was not alone in the room. After he died, I was. It was that simple.

I am alone now. His memorial service has come and gone. He has been cremated. In the spring, I will scatter his ashes. I am almost through the bureaucratic routines required to settle the estate. I have signed innumerable documents. I have donated his clothes. I have given away the dresser and chair that I had put in his room. I don't want the memories that having them in my home would bring.

I am gradually superimposing happy memories over the final bleak ones. I watch videotapes of him being interviewed about his AD. His personality shone through. His courage, his spirit, his wit and his wisdom will always be with me.

I have his instructions to follow. He knew he was my all. He knew I would be devastated. But, earlier in this sad process, he told me very firmly what he wanted me to do. "Rebuild your life. Wear red. Go out and do something, anything, every day. Don't try not to cry. People will understand," he said.

***I am gradually superimposing happy memories over the final bleak ones. I watch videotapes of him being interviewed about his AD. His personality shone through. His courage, his spirit, his wit and his wisdom will always be with me.***

As I sit here and type, I am crying. This evening, I will be attending a "Ladies' Night" at my church and I am wearing my new watch. It has a red wristband.

**Please look for Roberta's final entry, *Chapter 10: Luncheon Conversation* in the next issue of *The Canadian Review of Alzheimer's Disease and Other Dementias***

Alzheimer Society
CANADA

News from the Alzheimer Society of Canada

# Alzheimer's Disease is Not a Normal Part of Aging

*By Jack Diamond, MD, PhD*

One hundred years ago, Dr. Alois Alzheimer described to an audience of pathologists and clinicians the plaques and tangles he had observed in the brain of his recently deceased patient. Although his proposal was accepted that these pathological appearances were responsible for the patient's dementia, and despite this particular dementia being later distinguished from other dementias by bearing his name, most clinicians, including Alzheimer, continued to refer to the disease as pre-senile dementia or, in older people, senile dementia.

This unfortunate fact is almost certainly one explanation for the long-standing belief, which (surprisingly to this writer) some still hold, that Alzheimer's disease (AD) is an inevitable consequence of aging.

There is an argument that everybody would get AD if they lived long enough, including very elderly people who appear to have escaped it. This is a spurious argument deriving from purely statistical reasoning. It puts AD in the same category as dying! It assumes an inevitability based on the mathematical extrapolation of the curve relating age and incidence of AD. It does not allow, first, for the existence of aged people destined not to get AD; nor, second, for the possibility that the disease can be cured.

Nobody doubts that the biggest risk factor in AD is aging. Even in the five to seven percent of those who have the familial form of AD (FAD), the presence of the genes, that are unambiguously known to precipitate the condition, are not enough on their own; a minimum degree of aging has to have occurred as well (people carrying the suspect genes do not get AD when they are 15 years old!).

There have been a number of recent findings that appear to complicate the situation. First of all, numerous plaques (and to a lesser extent tangles) are a common occurrence in the brains of elderly people who die without ever having shown any signs of dementia whatsoever. Furthermore, AD, and in particular a condition thought by many to be a precursor of AD—Mild Cognitive Impairment—is now being diagnosed in younger people. As well, despite its increasing incidence, the majority of elderly people do not get AD.

Can these findings be reconciled? The inevitable conclusion has to be that AD cannot be a simple consequence of aging. Indeed, AD is only one among a number of clinical conditions whose occurrence is very much a function of aging. Here one thinks of bone fracture after falls, stroke, diabetes, cancer, and other age-related diseases. But these are not thought of simply as inevitable consequences of aging, any more than mumps, chicken pox and measles are inevitable consequences of being a child! It may be belabouring the point, but it has to be said that the expression "diseases of aging" is as informative and correct as the expressions "diseases of women" or "diseases of children."

What should be solved now, and indeed has the attention of many medical scientists, is the mystery of the missing pieces that must be added to Alzheimer's plaques and tangles in order to understand AD in its entirety: for example, to understand the exact links between the well-recognized risk factors (aging being the most important one), the observed brain pathology, and the observed dementia. One much-supported activity is the search for still to-be-identified risk factors for the disease, which could be genetic or environmental, for example.

All the known risk factors for AD increase with age (such as diabetes, obesity, high blood pressure, high cholesterol, episodes of depression, even the chances of random falls with concussion) and, unfortunately, all of the intrinsic repair mechanisms in the brain (indeed, in all of the body's organs) capable of withstanding these and other risk factors become less and less effective with age.

Many diseases, of which AD is but one, appear to take hold when the risk factors (which often include invading organisms or environmental or metabolic toxins) overcome the body's innate defense mechanisms. Age is a risk factor for a number of disorders as already mentioned. While aging is indeed inevitable, AD is not. AD is a disease and to deny this fact is to discourage the drive to search not only for a means of ameliorating it, but to cure it.

This year, the Alzheimer Society is recognizing the 100th anniversary of Dr. Alois Alzheimer's identification of the disease named in his honour. Throughout 2006, the Alzheimer Society will be reminding Canadians of this important anniversary and educating them about AD. To learn how the Society is commemorating the anniversary, please visit ***www.alzheimer.ca/english/newsevents/awareness.htm.***

*Dr. Jack Diamond is the scientific director of the Alzheimer Society of Canada. He is also Professor Emeritus in the Department of Psychiatry and Behavioural Neurosciences at McMaster University in Hamilton. He was formerly Associate Director for Scientific Affairs at the Montreal Neurological Institute at McGill University and was the founding chair of the original Department of Neurosciences when the new medical school was established at McMaster University.*

## 2006 National Conference

The Alzheimer Society of Canada's November 2006 Conference will highlight advances in research and innovation. "Alzheimer Research and Innovation: Yesterday, Today, Tomorrow" takes place at The Westin Harbour Castle in Toronto. Information about the conference is posted on our website *at www.alzheimer.ca*.

***The Alzheimer Society of Canada is a not-for-profit health organization dedicated to helping people affected by Alzheimer's disease. The Society provides support and educational programs for people with Alzheimer's disease and their caregivers. The Society also funds research into finding the causes and cure of the disease, and into improved methods of caregiving. The Society consists of a national office, 10 provincial organizations and more than 140 local groups across the country.***

***For more information on Alzheimer's disease and related dementias, Alzheimer Society programs and services, and how you can help, contact your local Alzheimer Society or visit the Society's website at www.alzheimer.ca or call 1-800-616-8816.***