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ALZHEIMER'S DISEASE

Sonya Norris
Science and Technology Division

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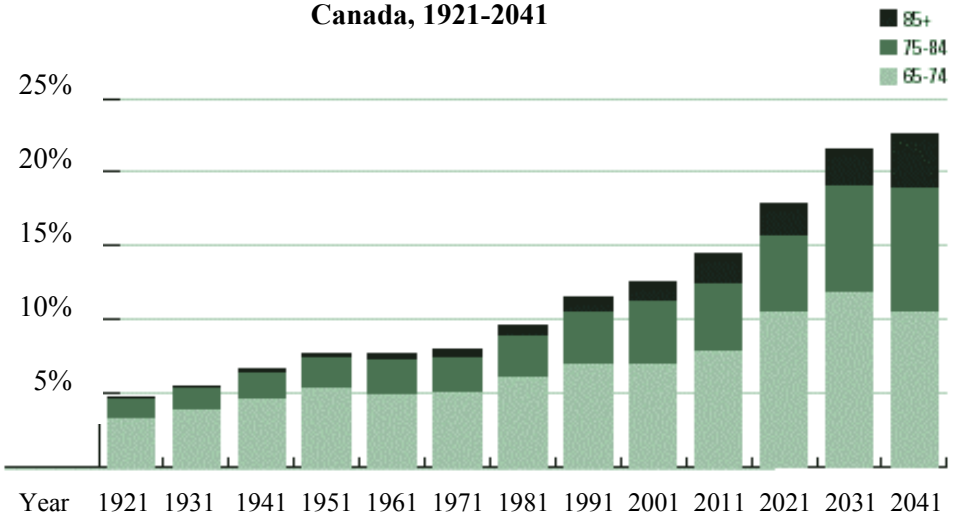
BACKGROUND

With the elimination of many diseases, particularly those affecting children and the young, Canadians are living longer. The percentage of Canadians over age 65, only 4% in 1900, is now 12.6% and is expected to increase to 20% by the year 2026. The graph below illustrates the increasing proportion of Canadians aged 65 and over.[1] This growth in longevity has brought with it a great increase in diseases and disorders that cause dementia,[2] the most common of which is Alzheimer's disease (AD), first identified in 1907 by Alois Alzheimer,[3] a German neuropathologist.

Seniors by age sub-groups, as % of the total population, Canada, 1921-2041



Source: *Canada's Aging Population*, Health Canada, 2002, p. 3.

(1) *Canada's Aging Population*, Health Canada, 2002, p.1.

(2) Dementia is the deterioration of the intellectual, emotional and cognitive faculties to the extent that daily function is impaired.

(3) Serge Gauthier, "Advances in the pharmacotherapy of Alzheimer's disease," *Canadian Medical Association Journal*, vol. 166, no. 5, March 2002, pp. 616-622.

This paper will review some of the major aspects of this devastating disease. It will also discuss the research efforts under way throughout the world to establish the cause(s), prevent the onset of AD, develop an effective method of diagnosis, engineer effective treatments, and discover a cure.

WHAT IS ALZHEIMER'S DISEASE?

A. Clinical Description

Alzheimer's disease is a progressive degenerative disorder of the cerebral cortex that produces dementia in middle to late life. Two main variants of the disease are known. Early-onset AD, which strikes victims in their 40s and 50s, accounts for only a small percentage of AD victims. Late-onset AD appears after age 65 and is the most common form of the disease. One form of early-onset AD has been found to be caused by a single gene mutation; this form of AD, however, accounts for only a tiny percentage of the total number of AD cases. The causes of the remainder of the early-onset and all of the late-onset forms of AD have not been conclusively identified. Research to discover effective treatments has had only limited success.

Clinically, AD results from a progressive loss of neurons from the cerebral cortex and other brain areas. The brain of a person who has died from this disease has two characteristics: neuritic plaques (clumps of β-amyloid protein outside the brain cells, or neurons), and neurofibrillary tangles (twisted, spaghetti-like fibres inside damaged neurons). Biochemical abnormalities associated with neuron failure include deposition of amyloid protein in cerebral blood vessels and senile plaques; disrupted nerve-cell-membrane phospholipid metabolism; and decreases in neurotransmitter substances such as acetylcholine, serotonin, norepinephrine, and somatostatin. It is extremely difficult to diagnose this disease without a biopsy, since other conditions, many of which are treatable, can have the same initial symptoms.

B. Progression

Memory loss is the most prominent early symptom of AD, followed by a slow disintegration of personality and physical control. As the disease progresses, 10% to 15% of patients hallucinate and suffer delusions, 10% have seizures and, in the late stages, 10% will become violent. The change in personality and temperament can be rapid. The rate of progression

of the disease varies among patients, with the average time from diagnosis to death ranging from eight to twelve years. The family usually cares for a patient at home for an average of four to five years. Total nursing care is necessary in later stages of the disease.(4)

Measures of global and cognitive dysfunction associated with the three stages of Alzheimer's disease(5)

Stage	Duration (yr)	Global Deterioration Score*	MMSE score†	Global autonomy
Mild	2-3	3-4	26-18	Independent living
Moderate	2	5	10-17	Supervision required
Severe	2-3	6-7	0-9	Total dependency

* Measures progressive need for assistance in daily activities (e.g., choosing clothes, dressing); scores range from 1-2 (normal) through 6-7 (severe dysfunction).
† This 22-item mini mental state exam scale measures cognitive function; scores range from 30 (excellent function) to 0 (severe dysfunction).

C. Diagnosis

This disease frequently masquerades as other ailments. Its diagnosis remains difficult, and no clinical test specific to this type of dementia has yet been developed. A complete medical team is involved in the evaluation process, which begins with eliminating the other possible causes of such symptoms as impaired intellectual functioning, memory loss, difficulty in recognizing or recalling the names of objects, and impaired ability to distinguish the relationships of objects. The evaluation encompasses medical, neurological and psychiatric examinations, a detailed history of the patient (including a complete inventory of all the drugs he or she takes) and various tests. Once a patient has been diagnosed as having AD, any change in his or her condition must be brought to the attention of the attending physician.

(4) Gauthier (2002).

(5) *Ibid*., p. 617.

THE MAGNITUDE OF THE PROBLEM

A. Number of Sufferers

Although the disease is not of epidemic proportions, the estimated number of Canadians living with AD in 2001 was 268,000 while almost 400,000 suffered from either AD or a related dementia.(6) Roughly 7% of those over the age of 65 have AD; with continuous growth in the percentage of Canadians over age 65, the number of people affected could exceed three-quarters of a million by the year 2031. Many studies have been undertaken to determine the incidence and prevalence(7) of the disease. Although the percentage of the population suffering from AD has been found to fluctuate between studies and countries, the exponential rise in both incidence and prevalence are quite consistent. It is generally agreed that there is a doubling in both parameters for every five years after age 65.(8)

B. Direct Costs

The human and financial costs of this affliction are enormous. The process of decline takes many years, during the first few of which family members often take care of the patient. Caregivers frequently retire early from paid employment to look after their relative, particularly as the disease progresses. Even when patients are being cared for at home, they frequently require costly medical and other care. The immediate family members, particularly the caregivers, also require help to enable them to cope with this "36-hour day."

The suffering associated with AD is dreadful, as much for those watching a loved one's slow decline as for the patients, who may suffer more by being aware of their eventual plight. Since the progression of the disease varies, the rapidity with which individuals lose their abilities differs. Even though memory is lost, the relationship between the patient and the family can to some extent be maintained over a period of time, as feelings and emotional responses continue; but as the disease progresses, a victim of AD eventually becomes only a "shell." The grief of the

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(6) Alzheimer Society of Canada Internet site at: http://www.alzheimer.ca/english/disease/stats-people.htm.

(7) Incidence is the number of new cases, usually per year. Prevalence is the number of people living with AD at a particular time.

(8) Ian McDowell, "Alzheimer's disease: Insights from epidemiology," *Aging: Clinical and Experimental Research*, vol. 13, no. 3, 2001, pp. 143-162.

person's immediate family continues, however, though society and friends do not always understand this.(9)

Even when using the most conservative estimates of the average number of years spent in an institution, typically three to four years, and the number of afflicted Canadians, the costs to the health care system are immense. Estimates of the annual public costs include homecare, institutions, medications, community support and the medical team, and range from $9,451 for mild AD to $16,054 for mild to moderate, $25,724 for moderate, and $36,794 for severe. This amounts to approximately $5.5 billion annually.(10)

CURRENT PRACTICE

A. Treatment and Care

Once a patient has been diagnosed as having AD, an assessment is made of the disease's stage of progression and of the strengths and weaknesses of the patient and the patient's family. Several assessment systems are available to evaluate the level of dysfunction in various areas. Based on this assessment, a comprehensive care plan is prepared by a team consisting of a family member, the paid caregiver with primary responsibility for direct care, other care providers, and the patient's physician.

1. Medical Interventions

Although a wide range of treatments has been tested, most have had limited effectiveness. There are now some medications available that can slow progression of the disease. It has been known since the 1970s that the brains of AD patients are deficient in the neurotransmitter chemical acetylcholine. Among the different types of drugs that affect cholinergic neurotransmission, only the cholinesterase inhibitors have been effective in treating the symptoms of AD. These inhibitors slow down the biochemical dismantling of acetylcholine and therefore theoretically prolong neurotransmission. Inhibition of the cholinesterases somehow modifies the formation of β-amyloid plaques, although the mechanism is not known. Three cholinesterase inhibitors have been safe and effective at slowing the progression of AD:

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(9) Dr. William Eaton, "Unresolved Grief of Family Members of Alzheimer Victims," *OANHSS Quarterly*, April 1989, pp. 5-8.

(10) Alzheimer Society of Canada Internet site at: http://www.alzheimer.ca/english/disease/stats-costs.htm.

donepezil, rivastigmine and galantamine. All three drugs appear to improve cognitive and global functioning for at least six months, perhaps for as long as a year. Throughout the progression of the disease, and depending on the needs of the patient, a wide range of expensive medication, such as psychoactive drugs to lift depression and sedatives to control violence, may be required.(11)

A new drug called memantine received approval by the European Commission in 2002 for use in moderately severe to severe cases of AD; however, it is not yet approved in North America. Memantine appears to protect the brain's nerve cells against excess amounts of glutamate, a messenger chemical released in large amounts by cells damaged by Alzheimer's disease or certain other neurological disorders. The attachment of glutamate to cell surface "docking sites" called N-methyl-D-aspartate (NMDA) receptors permits calcium to flow freely into the cell, which in turn may lead to cell degeneration. Memantine may prevent this destructive sequence by adjusting the activity of glutamate.(12)

2. Non-medical Interventions

Simple changes in the home can make life much easier for sufferers, help them maintain self-esteem and a degree of independence, and prolong the period in a home environment. Examples of low-cost changes and modifications to the environment include: reducing the noise levels in the home (noises from television, radio, and telephone as well as from speaking); avoiding vividly patterned and striped rugs, drapes and upholstery; placing locks up high or down low on outside doors and adding simple doorknob alarms; clearing floors of throw rugs and clutter; and reducing the contents of closets to simplify choices. These costs are generally paid for by the patient's family. Many of these, and other more expensive, modifications are introduced in long-term care settings. They aim at meeting the safety and security needs of the patient, reducing his or her confusion and contributing to the effective functioning of both patients and caregivers.

The well-being of the patient and his or her family is assessed every six months. In response to changing needs, the extent and nature of the care are modified, normally in consultation with the family. Other issues that may arise during the care of AD sufferers are assessment of the person's competence, power of attorney, and prevention of and response to abuse of both the patient

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(11) Gauthier (2002).

(12) From a fact sheet on the Alzheimer's Association Internet site at: http://www.alz.org/ResourceCenter/FactSheets/FSMemantine.pdf.

and the caregiver. Eventually the patient's condition deteriorates to the point where home care is no longer possible and he or she must be moved to long-term institutional care.

B. Support for Caregivers

Until an eventual cure and treatment for AD are found, this disease will remain a significant problem for Canadian society. Care, support and information for AD victims and their families come primarily from the health care system and from the Alzheimer's Society, which in Canada is organized at the national, provincial and, frequently, the municipal level. The information and support the society provides are crucial, particularly for the caregivers.

The caregiver needs information on the disease, including details of dementia and appropriate methods of care. The victim may become restless or suspicious, may wander, or have erratic sleep patterns. Such behaviour places an additional strain on the caregiver. Some studies have shown that caregiver depression and inappropriate living arrangements were the factors most associated with violence towards AD victims.(13) The caregivers themselves often suffer from depression or "burnout" and their health deteriorates as a result of trying to help the AD victim. Frequently, conflicts with attitudes and actions of other family members can greatly increase the risk of depression for caregivers. AD support groups offer families the emotional, spiritual and practical help they need to cope with the disease. The caregiver has many needs, including regular and increasingly lengthy relief from duties. The greater the level of support, the longer a caregiver can cope with the patient.

CURRENT RESEARCH

A. Causes of Alzheimer's Disease(14)

A definite link has been established between AD and the appearance of the "plaques and tangles" described earlier; the cause of their appearance, however, remains poorly understood. Further, the observation that some identical twins have exhibited different predispositions to developing AD suggests that causation is more complex than mere genetics.

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(13) Gregory J. Paveza et al., "Severe Family Violence and Alzheimer's Disease," *Gerontologist*, August 1992, pp. 493-497.

(14) Peter H. St George-Hyslop, "Piecing Together Alzheimer's," *Scientific American*, vol. 283, no. 6, December 2000, pp. 76-83.

The hallmark lesions of AD are the senile plaques (β-amyloid plaques) and neurofibrillary tangles. Although the appearance of a small number of tangles is a universal consequence of aging, their increased number and specific distribution in the brain help to define the stages of this disease. The neurofibrillary tangles are aggregates within the nerve cells (neurons) of a protein called tau that has undergone an aberrant modification, called phosphorylation. It is as yet unclear why the tangles lead to, or contribute to, dementia. One theory is that the accumulation of tau results in a malformation of the microtubules that transport nutrients and chemicals for neurotransmission; the malformation, in turn, reduces nutrient and neurotransmitter transportation and ultimately causes neuronal cell death.

The senile plaques occur outside of the brain cells, unlike tangles, and are deposits of amyloid material, a glycoprotein (protein complex attached to sugar units). These plaques appear long before the tau tangles. They are found in the brain of cognitively intact people as early as the fifth decade of life. By the eighth decade, as much as 75% of the population is affected. Dementia is believed to be associated with the density of these plaques, and their distribution in the hippocampus and cerebral cortex is specific to AD patients.

Although the manner in which these plaques and tangles produce cognitive decline is still poorly understood, it is generally agreed that these are the structures responsible for causing AD. But what causes these structures to form their destructive aggregates? Several risk factors and protective factors have been identified, although many remain as yet unconfirmed.

1. Risk Factors[15]

Four risk factors are firmly established for the development of AD. These are: age, the presence of the apolipoprotein E (ApoE) ε4 allele,[16] familial history of AD, and Down's Syndrome.

Aging – There is an exponential rise in the prevalence and incidence of AD with age, doubling every five years after the age of 65. The mechanisms that may be responsible for this drastic rise are as yet theoretical. The first is that mutations in messenger ribonucleic acid (RNA) have been identified in elderly people. Messenger RNA is the "middle man" between the

(15) See McDowell (2001); David G. Munoz and Howard Feldman, "Causes of Alzheimer's disease," *Canadian Medical Association Journal,* vol. 162, no. 1, January 2000, pp. 65-72; and C. J. Gilleard, "Is Alzheimer's disease preventable? A review of two decades of epidemiological research," *Aging and Mental Health*, vol. 4, no. 2, 2000, pp. 101-118..

(16) Alleles are different forms of the same gene.

gene and its protein. The second theory is that free radicals produce a build-up of oxidative damage with age. Free radicals (reactive oxygen species) are a naturally occurring product of cellular respiration. The body has its own mechanisms to neutralize these products; some cause oxidative damage before they can be stopped, however, and this damage accumulates with age. There is evidence associating AD with an accumulation of oxidative damage to proteins. In addition, it is believed that the toxic effects of β-amyloid are due at least in part to its release of free radicals. Environmental factors may also contribute to the risk associated with age, as these may accumulate with exposure.

ApoE ε4 – ApoE ε4 is the next major risk factor for the development of AD. Apolipoprotein E (ApoE) is involved in the repair and maintenance of neuron synapses, required for proper communication between neurons. The ApoE gene, found on chromosome 19, has three allelic forms: ApoE ε2, ApoE ε3, and ApoE ε4. The ε4 variety is associated with a significant increase in risk for developing AD. It appears to have a role in promoting the secretion of the insoluble β-amyloid peptide (called Aβ42) that is found in senile plaques. Like advanced age, the ApoE ε4 allele is neither necessary nor sufficient in itself to cause AD, and is therefore considered a risk factor rather than a cause.

Familial aggregation of AD cases – It has been clearly established that early-onset familial cases of AD are attributable to mutations to the β-amyloid precursor protein (β-APP) gene on chromosome 21, to the presenilin 1 gene on chromosome 14, or to the presenilin 2 gene on chromosome 1. Early-onset AD, however, accounts for only a very small proportion of all AD cases. Late-onset AD (after age 65) accounts for most AD cases. Of the late-onset AD cases, about 30% have a family history of the disease, with at least one first-degree relative affected. The associated risk appears to decrease with increasing age of disease onset.

Down's Syndrome – It is known that people with Down's Syndrome invariably show at least some features of Alzheimer's by the age of 40. In Down's Syndrome there are three copies of chromosome 21, instead of the normal two, and one of the mutations identified as a risk factor for AD is on the β-APP gene on chromosome 21.

Several other risk factors have been identified but are not yet fully scientifically validated. Among these are gender, head trauma, smoking, and depression. Aluminum, once thought to be a candidate risk factor, is no longer thought likely to increase the likelihood of

developing AD. However, increased aluminum exposure in people already developing amyloid plaques may hasten neuronal death.

Gender – Many, although not all, countries report a higher incidence of AD among women than men. One of the explanations for the perceived increase of AD among women is that women tend to live longer than men, increasing the chance of eventually developing the disease. Conversely, if it is established that women have a greater chance of developing AD than men, then perhaps some of the risk and protective factors discussed below could explain it, such as education, estrogen, physical activity and depression.

Head trauma – There is evidence to suggest that head trauma may hasten progression of AD. Plaques and tangles have been reported in the brains of boxers who had dementia. Also, it has been shown that as much as 30% of people who died following severe head trauma had cerebral plaque formation. The percentage is even greater for those carrying the ApoE ε4 allele.

Depression – A history of depression is thought to increase the likelihood of developing late-onset AD. The association between depression and AD is still unclear and requires specific testing. It does not appear as though AD is a product of anti-depressant use. Depression may be a physical response to cognitive decline, or it may trigger clinical assessment, which may in turn identify dementia in earlier stages than might otherwise have been identified.

Smoking – While some earlier studies suggested that smoking may have a protective effect against AD, recent studies have shown either no association, or a moderate risk for AD. One observation is that, as smokers tend to die earlier than non-smokers, progression to dementia and AD is less likely. In terms of being a risk factor, smoking exposes the brain (and the rest of the body) to more oxidative damage because of the free radicals produced in the process.

Occupational exposures – There appears to be an association between AD and occupational exposure to solvents, glues, pesticides and fertilizers. It is possible that this association is related also to education, as highly educated persons would not tend to share these occupational exposures (see protective effect of education, below). Some studies, however, have indicated that these risk factors are not connected.

Homocysteine – Homocysteine is an amino acid that is believed to be toxic to the lining of blood vessels when present in high concentrations in the blood, leading to vascular disease and increasing the chances of heart attack and stroke. It is also believed to contribute to

the development of AD. The micronutrients vitamin B6, vitamin B2 (riboflavin), vitamin B12 and folic acid all contribute to metabolizing homocysteine into less toxic metabolites. Increasing nutritional intake to include these vitamins may have a slowing effect on the symptoms of AD. Smoking is believed to be strongly associated with high homocysteine levels, as are low estrogen levels and high blood pressure.

High cholesterol/high blood pressure – An evolving area of study suggests that vascular disease and dementia are related, although not all research substantiates this hypothesis. It has been proposed, however, that a history of high blood pressure and/or high cholesterol levels increases the chance of developing Alzheimer's.

It should be noted that a recent article(17) found no statistical significance for many of the above parameters of risk factors.

2. Protective Factors(18)

Education – Many studies(19) have suggested that education may help to protect against AD. This protection is hypothesized to come from two different avenues. First, there may be greater neural development with a higher level of education. For individuals with a greater number of neurons, the loss of some (i.e., neuronal death) would have less impact. The second theory is that those individuals who have more education tend to remain intellectually active throughout their lifetime, compared to those with little or no education.

Estrogen – Although there has been conflicting evidence regarding the protective effect of estrogen against the development of AD, recent evidence suggests that estrogen does in fact afford some protection, provided that the woman does not carry the ApoE ε4 allele. The fact that this protective effect falls off sharply after menopause may also help to resolve the frequently cited observation that women are at greater risk of AD than men. Possibly estrogen (hormone replacement) therapy for post-menopausal women could eliminate this gap.

Non-steroidal anti-inflammatories (NSAIDs) – The reduced prevalence of AD among long-term NSAID users has been documented, particularly among arthritic patients.

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(17) Joan Lindsay et al., "Risk Factors for Alzheimer's Disease: A Prospective Analysis from the Canadian Study on Health and Aging," *American Journal of Epidemiology*, vol. 156, no. 5, 2002, pp. 445-453.

(18) See McDowell (2001) and Gilleard (2000).

(19) Terri Needels and Toby Bilanow, "Power up your brain," *Psychology Today*, July/August 2002, pp. 44-51.

Until recently, the manner in which NSAIDs provided protection against AD was unclear. However, it has now been shown that certain NSAIDs affect the production of β-amyloid, reducing the ratio of the β-amyloid peptide (Aβ42), found in senile plaques, to that of the Aβ40 peptide, which seems less likely to form plaques. It is believed that mutations in the APP gene may produce this effect. The NSAIDs found to reduce the proportion of Aβ42 to Aβ40 are ibuprofen, indomethacin and sulindac sulphide. (The most common NSAID, aspirin, was found not to affect the ratio.) These compounds are thought to reduce the amount of Aβ42 formed by selectively inhibiting the enzyme complex (called γ-secretase) involved in cleaving the APP gene.(20) This discovery could form the basis of new treatments for AD.

Immunization – Changes in the immune system have been implicated in some age-related disorders such as AD. Recent findings suggest that the role of the immune system in AD can also be provided by immunization. The Canadian Study of Health and Aging analyzed the incidence of AD with respect to patient history of immunization. It found that there was a significant reduction in risk of AD when there had been vaccination against diptheria, polio and tetanus.(21)

Protective genes – Although no specific genes that protect against AD have been identified, epidemiological studies have shown that some native north American populations are at lower risk for AD than most other populations. Examples include some Cree and Cherokee tribes. This phenomenon may be related to the lower rate of AD in Asiatic populations that has been noted in some studies.

Intellectual Activity – This protective factor appears to be closely related to the role of education in protecting against the development of AD. There is a direct correlation between amount of education and amount of intellectual stimulation throughout life. Remaining intellectually active in later years may have a protective effect by "teaching" the brain to be efficient and thereby increasing its tolerance of neuronal death.(22) This hypothesis is supported by the observation that significant amounts of plaques and tangles have been found on the brains

(20) Sascha Weggen et al., "A subset of NSAIDs lower amyloidogenic Aβ-42 independently of cyclooxygenase activity," *Nature*, vol. 414, November 2001, pp. 212-216.

(21) Réné Verreault et al., "Past exposure to vaccines and subsequent risk of Alzheimer's disease," *Canadian Medical Association Journal*, vol. 165, no. 11, 2001, pp. 1495-1498.

(22) R. S. Wilson et al., "Participation in cognitively stimulating activities and risk of incident Alzheimer disease," *Journal of the American Medical Association,* vol. 287, no. 6, February 2002, pp. 742-748.

of cognitively healthy seniors. However, a similar amount of plaques and tangles on the brains of less intellectually stimulated seniors was associated with cognitive impairment.(23)

Physical Activity – There is evidence to suggest that people who remain physically active are at lower risk of developing AD. The reason for this protective effect is still unproven. However, it may be that those who are physically active also tend to stay intellectually active, or it may be because physical activity increases blood flow to the brain, increasing nutrient and oxygen delivery to neurons and keeping them healthy.

Alcohol Consumption – Some studies have suggested that wine, in moderate amounts, may have a protective effect against AD. Although other studies have not been able to substantiate this finding, it may be that protection is offered by the anti-oxidant qualities of wine. (The effects of oxidative damage are discussed above under the "aging" category.)

B. Diagnosis

Now that science has elucidated various factors that may increase or decrease the probability of developing AD, early diagnosis can be less a cause of despair and more a starting-point for action. That is, perhaps progression of the disease can be slowed down with early diagnosis, followed by intellectual and physical exercise, hormone therapy, treatment for depression, smoking cessation, and other factors that may prove to affect the disease.

A number of areas are under investigation as methods for early diagnosis of Alzheimer's. Recently it was discovered that certain areas of the brain show atrophy as much as three years before the onset of AD symptoms. This atrophy can be detected by magnetic resonance imaging (MRI).(24) The limitation of this method may be that it could prove difficult to differentiate between atrophy due to AD or other types of dementia.

Another diagnostic tool being developed involves positron emission tomography (PET) scans. Using this type of scan, investigators have found that there is a reduced glucose metabolism in a specific area of the brain called the entorhinal cortex in patients with mild cognitive impairment. This is still being researched and may have the same limitation as that

(23) See Needels and Bilanow (2002).

(24) Kristin Leutwyler, "Toward Early Diagnosis of Alzheimer's Disease," *Scientific American*, vol. 285, no. 2, August 2001; Ingmar Skoog, "Magnetic resonance imaging to assess Alzheimer's disease," *The Lancet*, vol. 359, May 2002, pp. 1538-1539.

just mentioned for MRI, in that it may be difficult to distinguish between AD and other dementias.

Other new research may provide a diagnostic method more suited to distinguishing between Alzheimer's and other dementias. Recently cited work in mice explores a possible blood test for diagnosing AD.(25) Should it prove applicable to humans, this method would include a simple blood test following an injection of an antibody to β-amyloid peptide.

Perhaps the most promising as a non-invasive diagnostic advance is the possibility of a urine test reported in June 2002.(26) The method is still in the development stage, but researchers are optimistic that it will soon be widely available. The proposed test would measure the level of a substance in the urine that is produced due to increase oxidative damage in the brain. This has been tested in patients but is not yet validated as a diagnostic tool.

C. Symptomatic Treatment(27)

Until the definitive cause of AD and the mechanism involved in it are discovered, the disease itself cannot be cured. The current treatment consists mainly of palliative care and maintenance of the patient once progression of the disease can no longer be prevented. Several new developments for treating the symptoms have been announced, and further testing and evaluation are needed.

In addition to the therapeutic targets identified through risk and protective factors against AD, other substances are showing promise for arresting, slowing and possibly reversing the signs of AD. Statins – drugs prescribed to lower low-density lipoprotein (LDL) cholesterol – are now showing a link with reduced risk of AD. Studies analyzing the effect of statins on progression of AD have reported a reduced production of β-amyloid.

Another area of therapeutic progress involves apolipoprotein E, the risk factor mentioned earlier. It has been shown that ApoE is decreased in the brains of AD patients, and that some agents such as probucol can reverse this. Other research is indicating that any ApoE

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(25) Ronald B. DeMattos et al., "Brain to Plasma Amyloid-β Efflux: a Measure of Brain Amyloid Burden in a Mouse Model of Alzheimer's Disease," *Science*, vol. 295, March 2002, pp. 2264-2267.

(26) Domenico Praticó et al., "Increase of brain oxidative stress in mild cognitive impairment: a possible predictor of Alzheimer disease," *Archives of Neurology*, vol. 59, no. 6, June 2002, pp. 972-976.

(27) From the International Conference on Alzheimer's Disease and Related Disorders of July 2002, available on-line at: http://www.alz.org/internationalconference/highlights.htm.

therapeutic agent should probably be ApoE ε3-specific, so as not to promote, via the ApoE ε4 described earlier, secretions of the insoluble β-amyloid 42 peptide that is found in senile plaques.

Another possibility for new treatment involves the enzyme responsible for cleaving the amyloid precursor protein (APP). Presenilin genes encode a large, transmembrane enzyme complex called γ-secretase which cuts up APP and produces either the soluble Aβ40 or the insoluble Aβ42 variety. Inhibitors of γ-secretase are a possible therapeutic route to slowing, or arresting, the accumulation of plaques. Such inhibitors are in the earliest phases of development.

Perhaps the most exciting of the therapeutic developments is recent work suggesting that vaccination against β-amyloid peptide can stop the formation of plaques, and perhaps even reverse or prevent their accumulation. Phase I clinical trials were completed in 2000, but phase II trials were halted when 0.1% of patients who were in the trial experienced side-effects consistent with an autoimmune reaction. It is unclear whether trials will proceed with this or a similar drug. Similar work continues, however, using antibodies produced in response to specific regions of the β-amyloid peptide. Another approach to clearing away plaques involves studies that stimulate specific cells in the brain called microglia. In mice, microglia were stimulated with Transforming Growth Factor β1 (TGF-β1), causing the microglia to clear away the plaques. TGF-β1 itself cannot be used as a therapeutic agent because it has many effects in the body, but the molecules produced by the microglia in response to the TGF-β1 may be a therapeutic target.(28)

ISSUES TO RESOLVE

AD is an enormous social and economic problem. As the population ages, the number of victims is likely to increase steadily, imposing a massive burden on the health care system. Until a cure and an effective treatment are found, AD poses social, legal, and medical challenges as well as problems of scientific policy and resource allocation.

Social challenges include ensuring a uniform level of supplemental support for caregivers and optimizing the sharing of resources between expanded home care and institutional care. Legal issues include power of attorney for the victim, and voluntary euthanasia. Medical issues include a lack of available institutions for long-term care, particularly specialized units for

(28) Tony Wyss-Coray et al., "TGF-β1 promotes microglial amyloid-β clearance and reduces plaque burden in transgenic mice," *Nature Medicine*, vol. 7, May 2001, pp. 612-618.

AD sufferers, and the need for increased education and awareness on the part of the medical community.

Another problem is the relatively modest level of funding assigned to AD research in Canada. The Canadian Institutes of Health Research reports that it provided approximately $13.5 million in fiscal year 2001-2002 for all research related to AD.(29) This amount of research is minuscule when compared to the multi-billion dollars spent by Canadian taxpayers to treat the effects of AD.

HOPE FOR THE FUTURE

Research into the causes and treatment of AD has accomplished a considerable amount in the past decade; however, much remains to be done. Many researchers are confident that the causes of Alzheimer's will successfully be defined in the foreseeable future, so that appropriate prevention can be practised. In addition, development of new medicines and vaccines shows considerable promise in producing much better alternatives to the medications currently available.

(29) Personal communication; parameters of search included "Alzheimer's" and "dementia."