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ALZHEIMER'S DISEASE

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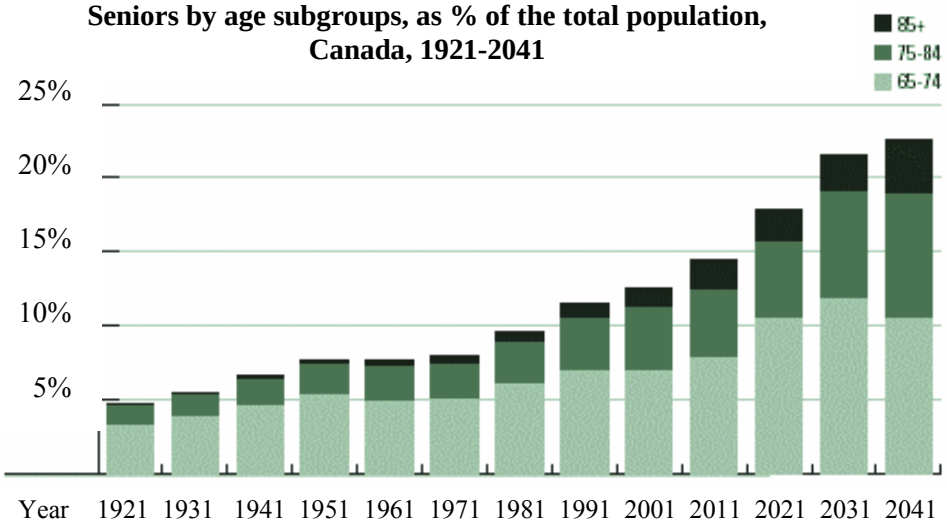
ALZHEIMER'S DISEASE

BACKGROUND

With the elimination of many diseases, particularly those affecting children and the young, Canadians are living longer.(1) The proportion of the Canadian population over age 65, only 4% in 1900, is now 12.6% and is expected to increase to 20% by the year 2026. Figure 1 illustrates this demographic shift.(2) The increase in longevity has resulted in an increase in the number of Canadians affected by conditions associated with dementia,(3) the most common of which is Alzheimer's disease (AD), first identified in 1907 by Alois Alzheimer,(4) a German neuropathologist.

Figure 1
Seniors by age subgroups, as % of the total population, Canada, 1921-2041



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

(1) This increased longevity, coupled with the aging of "baby boomers," has brought about an increase in the proportion of the population aged 65 years and older.

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

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

(4) Serge Gauthier, "Advances in the pharmacotherapy of Alzheimer's disease," *Canadian Medical Association Journal*, Vol. 166, No. 5, 5 March 2002, pp. 616-22.

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 or causes of AD, to prevent its onset, develop more effective methods 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 cases. 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 arise from a single gene mutation; this form, however, accounts for only a tiny percentage of the total number of 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 areas of the brain. Brain biopsies and autopsy studies reveal two characteristic features: 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 phospholipid metabolism in the nerve cell membrane; and decreased levels of neurotransmitters 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% become violent. The change in personality and temperament can be rapid. The rate of progression of the disease varies among patients, and the average time from diagnosis to death ranges from eight to twelve years (Table 1). Typically, family members care for affected individuals at home for an average of four to five years. Total nursing care is necessary in the later stages of the disease.[5]

(5) Gauthier (2002).

Table 1
Measures of global and cognitive dysfunction associated with the three stages of Alzheimer's disease(6)

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	9-0	Total dependence

* The Global Deterioration Scale measures progressive need for assistance in daily activities (e.g., choosing clothes, dressing); scores range from 1-2 (normal) through 6-7 (severe dysfunction).

† The 22-item Mini Mental State Exam measures cognitive function; scores range from 30 (excellent function) to 0 (severe dysfunction).

a. Source: Adapted from Gauthier (2002), p. 617.

C. Diagnosis

Alzheimer's disease frequently masquerades as other ailments. 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 the patient's symptoms, which may include impaired intellectual functioning, memory loss, difficulty in recognizing or recalling the names of objects, and impaired ability to distinguish the relationships between objects. The evaluation encompasses medical, neurological and psychiatric examinations, a detailed history of the patient (including an inventory of current medications) 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.

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 2007 was 300,000, while almost 450,000 suffered from either AD or a related dementia.(7) Roughly 7% of Canadians over the age of 65 have AD; therefore, the number

(6) Ibid., p. 617.

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

of people affected is projected to exceed three-quarters of a million by the year 2031. Many studies have been undertaken to determine the incidence and prevalence(8) of the disease. Although the percentage of the population suffering from AD has been found to fluctuate between studies and countries, the rapid 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.(9)

B. Direct Costs

The human and financial costs of this affliction are enormous. The process of decline takes many years. Caregivers frequently retire early from paid employment to look after their affected 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, both for those watching a loved one's slow decline and for the patient, who may be painfully aware of his or her prognosis. Since the progression of the disease varies, the rapidity with which individuals lose their faculties 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; however, as the disease progresses, victims of AD eventually become only a "shell" of their former selves. The grief of the person's immediate family continues, however, although society and friends do not always understand this.(10)

Even using the most conservative estimates of prevalence and of the average number of years spent in institutional care (typically three to four years), the costs to the health care system are immense. Estimates of the annual public costs per patient include costs for home care, institutional care, 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 AD. This amounts to approximately $5.5 billion annually.(11)

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(8) "Incidence" refers to the number of new cases occurring within a population during a given period (usually per year). "Prevalence" refers to the proportion or the number of new or existing cases within a population at a particular time.

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

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

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

CURRENT PRACTICE

A. Treatment and Care

Once a patient has been diagnosed with AD, an assessment is made of the stage of progression of the disease, the strengths and weaknesses of the patient, and the patient's family situation. 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 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 drugs slow the biochemical dismantling of acetylcholine and therefore, at least theoretically, prolong neurotransmission. Inhibition of the cholinesterases somehow modifies the formation of β-amyloid plaques, although the mechanism by which this occurs is not known. Three cholinesterase inhibitors have been found safe and effective in slowing the progression of AD: donepezil (Aricept), rivastigmine (Exelon) and galantamine (Reminyl). All three drugs appear to improve cognitive and global functioning for at least six months and 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.[12]

A newer drug called memantine (Ebixa) received approval by the European Commission in 2002 for use in moderately severe to severe cases of AD; however, it has received only conditional approval in Canada. 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 and certain other neurological disorders. The attachment of glutamate to molecular "docking sites" on the cell surface (i.e., N-methyl-D-aspartate

(12) Gauthier (2002).

receptors) permits calcium to flow freely into the cell, which in turn may lead to cell degeneration. Memantine may prevent this destructive sequence by regulating the activity of glutamate.(13)

2. Non-medical Interventions

Simple changes in the home can make life much easier for Alzheimer's sufferers, helping them to maintain self-esteem and a degree of independence, and prolonging the period that they can safely remain in their home environment. Examples of low-cost changes and modifications to the environment include: reducing noise levels in the home (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 current standard of care includes an assessment of well-being of the patient and his or her family 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 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 health care charities such as the Alzheimer's Society, which in Canada is organized at the national, provincial and, frequently, municipal level. The information and support the Society provides are crucial, particularly for caregivers.

The caregiver needs information on the disease, including details about the behavioural effects of dementia and about appropriate methods of care. The victim may become

(13) From a fact sheet on the Alzheimer's Association Internet site, http://www.alz.org/documents/national/FSMemantine.pdf.

restless or suspicious, may wander, and may 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 toward AD victims.(14) The caregivers themselves often suffer from depression or "burnout," and their physical health can also deteriorate as a result of trying to help the AD victim. Frequently, conflicts with the 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(15)

Although a link has been well established between AD and the appearance of the "plaques and tangles" described earlier, the cause of these features remains poorly understood. Studies involving identical twins suggest that causation is more complex than mere genetics.

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 and that this malformation, in turn, reduces nutrient and neurotransmitter transportation and ultimately causes neuronal cell death.

Unlike tangles, senile plaques occur outside of the brain cells. They 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.

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(14) Gregory J. Paveza et al., "Severe Family Violence and Alzheimer's Disease," *Gerontologist*, August 1992, pp. 493-7.

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

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 they remain as yet largely unconfirmed.

1. Risk Factors[16]

Five risk factors are firmly established for the development of AD. These are: age, familial history and genetics, diabetes, Down's syndrome, and mild cognitive impairment.

Aging – There is an exponential rise in the prevalence and incidence of AD with age, doubling every five years after the age of 65. Various mechanisms have been postulated as responsible for this drastic rise. One theory relates to the mutations in messenger ribonucleic acid (RNA) that have been identified in elderly people. Messenger RNA is the "middle man" between the gene and its protein. A second theory is that free radicals produce a buildup 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. Some evidence associates 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, given that free radicals may accumulate with exposure.

Familial History and Genetics – 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. There is a family history of the disease in about 30% of cases of late-onset AD, with at least one first-degree relative affected. The associated risk appears to decrease with increasing age of disease onset.

The ApoE gene is another major risk factor for AD. Apolipoprotein E (ApoE) is involved in the repair and maintenance of the neuronal synapses required for proper communication between neurons. The ApoE gene, found on chromosome 19, has three allelic[17]

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(16) 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.

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

forms: ApoE2, ApoE3, and ApoE4.[18] The ApoE4 allele is associated with a significant increase in risk for AD. It appears to have a role in promoting the secretion of the insoluble β-amyloid peptide (called Aβ42) found in senile plaques. Like advanced age, the ApoE allele is neither necessary nor sufficient in itself to cause AD, and is therefore considered a risk factor rather than a cause.

Diabetes – Type II diabetes is known to be a risk factor for AD. Dementia is more common in people with diabetes than in those without diabetes, and Alzheimer's is the most common of the dementias. The mechanism is unclear, but the insulin resistance characteristics of type 2 diabetes may increase the risk of Alzheimer's through inflammation of the central nervous system, regulation of the β-amyloid peptide, or damage to blood vessels from high glucose levels.

Down's Syndrome – It is known that people with Down's syndrome are at increased risk for Alzheimer's disease. 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.

Mild Cognitive Impairment – It is estimated that 85% of people with mild cognitive impairment (level of cognitive or memory impairment beyond that of normal aging) will develop Alzheimer's disease within ten years. Although this is sometimes described as an important risk factor for the disease, it can also be described in terms of an early symptom.

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

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.

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(18) These can also be referred to as ApoE ε2, ApoE ε3, and ApoE ε4.

Depression – A history of depression is thought to increase the risk of late-onset AD. The association between depression and AD is still unclear and requires specific investigation through research. It does not appear as though AD is a product of antidepressant 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.

Homocysteine – The amino acid homocysteine 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 help to break down 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 risk of AD.

It should be noted that the statistical significance for many of the above risk factors is still disputed.(19)

2. Protective Factors(20)

Education – Many studies(21) 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.

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 level of education and degree of intellectual stimulation throughout life. Remaining

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(19) 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. 445-3.

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

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

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 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)

Estrogen – Although there has been conflicting evidence regarding the protective effect of estrogen against the development of AD in women, recent evidence suggests that estrogen does in fact afford some protection in those who do not carry the ApoE4 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 reduce this gap.

Non-steroidal Anti-inflammatory Drugs (NSAIDs) – The reduced prevalence of AD among long-term NSAID users has been documented, particularly among arthritic patients. 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.(24) 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. 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 diphtheria, polio and tetanus.(25)

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(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. 742-8.

(23) See Needels and Bilanow (2002).

(24) Sascha Weggen et al., "A subset of NSAIDs lower amyloidogenic Aβ-42 independently of cyclooxygenase activity," *Nature*, Vol. 414, November 2001, pp. 212-6.

(25) 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. 1495-8.

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.

Physical Activity – There is some evidence to suggest that people who remain physically active are at lower risk of developing AD. The reason for such an association is unclear: it may be that those who are physically active also tend to stay intellectually active, or it may be that physical activity increases blood flow to the brain, increasing nutrient and oxygen delivery to neurons and keeping them healthy.

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 with early diagnosis, followed by intellectual and physical exercise, hormone therapy, treatment for depression, smoking cessation, and other interventions, as yet undiscovered, that may affect the disease.

A number of areas are under investigation as methods for early diagnosis. 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) as well as positron emission tomography (PET) scans.(26) The limitation of these methods may be that it could prove difficult to differentiate between atrophy resulting from AD and other types of dementia.

Other research may provide a diagnostic method more suited to distinguishing between Alzheimer's disease and other dementias. Experimental work in mice has explored a possible blood test for diagnosing AD,(27) although this has not been translated yet to human application. Another blood test being developed detects clumps of misfolded proteins characteristic of AD.(28)

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(26) 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. 1538-9.

(27) 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. 2264-7.

(28) Information available on the website for Amorfix Life Sciences, www.amorfix.com.

Perhaps the most promising as a non-invasive diagnostic advance is the possibility of a urine test reported in June 2002.(29) 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 because of increase oxidative damage in the brain. This has been tested in patients but is not yet validated as a diagnostic tool.

C. Symptomatic Treatment(30)

Until the cause of AD and the mechanism involved in its development are definitively known, 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 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 therapeutic agent should probably be ApoE ε3-specific, so as not to promote, via the ApoE4 allele 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.

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(29) 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. 972-6.

(30) Brian E. Leonard, "Pharmacotherapy in the treatment of Alzheimer's Disease : an update," *World Psychiatry*, Vol. 3, No. 2, June 2004, pp. 84-8.

Perhaps the most exciting of the therapeutic developments is recent work suggesting that vaccination against β-amyloid peptide may 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 has been tested in 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.(31)

ISSUES TO RESOLVE

AD is a significant social and economic problem. As the population ages, the number of victims is likely to increase steadily, imposing a large 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 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 funding has been slowly increasing over the years by 1-2 million per year (for all research related to AD), reaching approximately $22.2 million in 2006-2007.(32) The Alzheimer's Society of Canada spent $3 million in 2006 on research. This amount of research funding is small compared with the multi-billion dollars spent by Canadian taxpayers to treat the effects of AD.

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(31) 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. 612-8.

(32) Personal communication; parameters of CIHR funding database search included "Alzheimer's" and "dementia."

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, the development of new medicines and vaccines shows considerable promise in producing much better alternatives to the medications currently available.