



A Report on Alzheimer's Disease and Current Research

by Dr. Jack Diamond, Scientific Director
Alzheimer Society of Canada

Alzheimer *Society*



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Dr. Diamond received his PhD and subsequently his medical degree at the University of London, England, after which he did two years of post-doctoral research at Harvard Medical School, returning to a faculty position at University College London. He is widely published, having written more than 70 papers in refereed journals, and 15 book chapters.

The Alzheimer Society

The Alzheimer Society is a nationwide, not-for-profit health organization dedicated to helping people affected by Alzheimer's disease. The Society consists of a national office, 10 provincial organizations and more than 140 local offices across the country. The Society develops and provides support and educational programs and information for people with the disease, their families, caregivers and members of the health-care team. The Society is a leading funder of Alzheimer research in Canada.

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Introduction

For the past few years Dr. Jack Diamond has been making presentations on Alzheimer's disease research to various audiences across Canada and internationally. From these presentations, *A Report on Alzheimer's Disease and Current Research* has been created. The purpose of this report is to provide people who are not scientists or clinicians with easy to understand information on Alzheimer's disease, including risk factors, how researchers decide on the most promising ways to search for new treatments and where we stand in the search for a cure. To keep pace with the rapid advances in research, this report is updated periodically. This report focuses on the advancements made in biomedical research. A new companion report (in preparation) focuses on the equally important Social/Psychological research, which addresses the day-to-day issues that impact the quality of life for people with Alzheimer's disease, their caregivers and their families. This companion report will be available in the spring of 2008.



What is Alzheimer's disease?

Alzheimer's disease is the most widespread of a large class of disorders which clinically are known as "dementias", diseases characterized by a progressive deterioration of thinking ability and of memory. Alzheimer's disease is a disease of the brain, in which nerve cells die and their connections with other nerve cells are lost. It was originally regarded as a purely behavioral disorder, an inevitable decline in brain functions as one aged, just like the deterioration of the body and its ability to undertake physical activities. For that reason it was first called senile dementia. This view changed however, or at least began to change, when Dr. Alois Alzheimer published his description of senile dementia over one hundred years ago. After his female patient died in her early fifties with senile dementia he studied her brain tissue in the microscope, and observed the "plaques" and "tangles" which are now accepted as the hallmarks of the disease (we'll return to these later). The plaques are sometimes referred to as "amyloid plaques", "senile plaques", and "neurotic plaques". Some 3-4 years later, in his honour, senile dementia was renamed Alzheimer's disease. Somewhat surprisingly it took more than half a century for Dr. Alzheimer's message to sink in – that senile dementia was a genuine disease, in which nerve cells in the brain die due to the toxic effects of a number of abnormal ("pathological") changes that occur in the brain.

In most cases, the disease progresses slowly, but the rate of decline is extremely variable and changes from person to person. In many instances it may be preceded by a few years of Mild Cognitive Impairment (MCI), a condition in which true dementia is absent, but nevertheless memory and cognitive functions are detectably reduced (MCI is returned to later). In Alzheimer's disease, forgetfulness gradually increases, and in the later stages even close family members may fail to be recognized. The ability to carry out normal activities such as reading, driving, and cooking gradually decreases, as does the ability to make judgments and appropriate responses to everyday issues. There can also be behavioural changes such as agitation, aggression, depression, disturbances of balance and movement, and an inability for people to find their way even in familiar surroundings. In time the affected persons become unable to look after themselves and caregivers become essential for all aspects of daily living. Alzheimer's disease is ultimately fatal, and death usually occurs within seven to 10 years after diagnosis. The body is weakened by inactivity and muscle wasting, and a lowering of the body's immune functions makes bacterial and viral infections very common. This leads to the usual cause of death, pneumonia, hastened by the decreasing ability of the affected person to cough and generally to move about normally.

It is important to know that Alzheimer's disease is not a normal part of aging. The decline in memory and thinking ability reflect the progressive death of brain cells caused by the disease process. This is quite different from relatively minor brain cell loss that may occur naturally with aging, a loss which, until extreme ages are reached may only marginally affect memory and cognitive ability.

New studies of the incidence of Alzheimer's disease are in progress, but at present it appears that some 5-8% of Canadians over the age of 65 have Alzheimer's disease, rising to an alarming 30-50% of those over 85. While the vast majority of Alzheimer cases are of the sporadic or late onset form of Alzheimer's disease, about 5 to 7 per cent of the Alzheimer population are in the category called Familial Alzheimer's disease (FAD), which traditionally used to be called early onset Alzheimer's disease (due to the fact that people with FAD typically manifest symptoms earlier than those with sporadic Alzheimer's disease). FAD is identical to the sporadic form, but it is largely attributable to the inheritance of certain genes which at some point in that family tree mutated. This means that they changed their normal character to an abnormal one that didn't function properly, and because they were inherited entire families became susceptible to Alzheimer's disease. The discovery of these mutated genes has been critically important in furthering our understanding of all Alzheimer's disease, and in allowing scientists at long last to create animal models of the disease upon which potential treatments can be tested.

Are we experiencing an epidemic of Alzheimer's disease? Not really, but the numbers are increasing dramatically. This is attributable to the increasing ability of new diagnostic approaches to reveal Alzheimer's disease at earlier stages, to an aging Canadian population, and to the fact that the risk factors for Alzheimer's disease (see following) do genuinely appear to be on the increase. While all this makes it appear as though a new type of early onset Alzheimer's disease is appearing, this is not the case. The disease has not changed its character. It would be best to reserve the use of "early and late onset" Alzheimer's disease simply to describe the individual case, rather than the type of disease. Early onset Alzheimer's disease now should refer to people who develop the disease at ages significantly younger than 65 years and who are very likely to have the common sporadic form of Alzheimer's disease. Late onset Alzheimer's disease generally refers to people who develop the disease at ages over 65.

What causes Alzheimer's disease?

It's often stated that we don't know what causes Alzheimer's disease, but many are coming to the conclusion that in a sense we actually do. All the organs of the body, including the brain, have built-in self-repair mechanisms. Alzheimer's disease appears to develop when the combined effects of the known and still to be identified influences called "risk factors" cross a certain "threshold". At this point they overwhelm the natural self-repair and self-healing mechanisms in the brain that normally maintain the nerve cells in a healthy state. If this view is correct, then there is no specific cause of Alzheimer's disease, but rather it is the additive effects of multiple factors, with aging heading the list.

Oxidative stress and Alzheimer's disease

Oxidative stress refers to the threatening situation created when small molecules known as "reactive oxygen species" (ROS) begin to accumulate faster than the body can get rid of them, allowing them to exert their adverse toxic effects on cells everywhere in the body, including the brain. ROS are normal products of metabolism, and can even be used to beneficial ends, for example by the immune system as one way to kill invading organisms. However, as ROS build up they become damaging. Normally ROS are eliminated by special enzymes made by the body's cells, assisted by the intake in food of natural "anti-oxidants" such as vitamins C and E. But environmental stress, many diseases, some drugs, the "internal" stress generated whenever a person's health and well-being are threatened, probably most of the risk factors described below, and even A-beta itself (A-beta is the protein regarded as the principal culprit in Alzheimer's disease, as will become evident in the following sections), all act to increase the production of ROS, and to reduce the efficiency of their elimination by the body. This is oxidative stress. It's an important contributor to the deterioration of the body's tissues and cells in aging, and it's a major component of Alzheimer's disease. Oxidative stress, therefore, is a key target of Alzheimer treatments, among which a healthy lifestyle is paramount.



Risk Factors

These are characteristics of the person and the person's lifestyle and environment that contribute to the likelihood of getting the disease. While most risk factors are well established, some are still controversial. Many of the risk factors for Alzheimer's disease, like high cholesterol levels or high blood pressure, are risk factors for many other diseases as well. It is becoming increasingly recognised that most, if not all, of the risk factors help induce oxidative stress.

Aging

As indicated above, aging is the most important risk factor. Whatever other risk factors are present, Alzheimer's disease never sets in until some minimum adult age is reached. This age may be significantly younger for a person with FAD. An important consequence of aging is deterioration in the efficiency of the body's self-repair mechanisms. The deterioration occurs at different rates in different people, which may also explain in part why some people are more susceptible to getting Alzheimer's disease than others. While aging would appear to be the one risk factor that we can do least about, this may not be so. A huge amount of research is going into finding out what causes the progressive deterioration in aging of tissues and organs that include the brain (including the role of oxidative stress described above), and there is a genuine feeling among scientists that the answer is not beyond reach. There is solid evidence that in animals a rigorously controlled caloric restricted diet (CR), beginning at weaning, dramatically slows the aging process. While instituting an equivalent life-long CR in humans is just not possible, the fact that body aging can be influenced at all is a very important stimulus to scientific research on aging. The objective is not so much to prolong life as to prevent the slow decline in function during it. Everybody knows that some older people seem to have remarkably young brains, while in contrast, others seem to be old before their time. The point here is that from the perspective of Alzheimer's disease, it is not chronological age that matters but brain age, something we can recognize but so far cannot control. One encouraging item is that scientists are well on their way to understanding the brain's self-repair mechanisms, and are looking at ways to activate them when they seem to be switching off, as in aging.

Genetic risk factors

Aside from the already mentioned mutated genes heavily implicated in FAD, the most important genetic risk factor for the common sporadic Alzheimer's disease is the "apoE4" gene. In contrast to the genes responsible for FAD, this gene is not an abnormal one, i.e. it has not undergone a mutation that has impaired its ability to carry out its usual job. ApoE4 is one of the three variants of the apoE gene, the others being the benign apoE2 and apoE3 genes. Everybody has a double set of genes, one from each parent. If a person's pair of apoE genes include one apoE4 (inherited from one parent), they have three times the normal risk of developing Alzheimer's disease. However, if they carry two apoE4 genes (meaning one from each parent) the risk increases to ten times. That said, it is important to note that people with no apoE4 genes can still get Alzheimer's disease, just as people with two apoE4 genes can escape it. Having a parent or sibling with Alzheimer's disease increases one's risk two to three times, implying the likely involvement of genes not yet identified. Researchers are actively looking for evidence of other quite normal genes that predispose one to Alzheimer's disease, but it seems unlikely that these still to be discovered genes will be as important a risk as the apoE4 one. To date, more than a dozen gene variants have been identified that occur in people with Alzheimer's disease to a greater extent than in non-Alzheimer people, but as with the apoE4 gene, people can have Alzheimer's disease and not have these suspect variant genes. Researchers are especially interested in the evidence that some variant genes (like the recently discovered SORL1 gene) lead to a situation in the nerve cells that favors the production of the potentially dangerous A-beta protein (also called beta amyloid), about which more will be said later. Further research on these suspect genes could produce results that help chemists design drugs that would lessen the production of this threatening protein. Finally, a newly identified gene (GAB2) in its healthy form appears to protect the brain from developing tangles, but in a modified form found in the Alzheimer brain seems to promote the development of tangles inside nerve cells. Again, future research may be able to capitalize on these findings to design drugs that will oppose tangle formation.

In addition to aging and to genetic factors, all the following have been documented as risk factors for Alzheimer's disease:

- **Diabetes** – it has been known for some years that type 2 (adult) diabetes is a risk factor for Alzheimer's disease, in large part, it was assumed, because of the associated blood vessel and heart disorders, and sometimes obesity, that are known risk factors for Alzheimer's disease. It's also well established that glucose utilization is impaired in the brains of people with Alzheimer's disease, rather like the situation in the bodies of people with diabetes. New research techniques and brain imaging have now revealed that the impairment in the Alzheimer brain is probably because the brain is itself in a sort of diabetic state, and it has even been suggested that Alzheimer's disease be called "type 3 diabetes," even though the affected person may not be diabetic in the ordinary sense. It's now known that in type 2 diabetic people, the toxic protein implicated in plaques may be present in the pancreas (the organ that normally produces insulin), strengthening the suspected link between type 2 diabetes and Alzheimer's disease. In any event, it seems that in the Alzheimer brain either (i) the production of insulin (known to occur in brains) is reduced for some reason, in this regard resembling type 1 (juvenile) diabetes and/or (ii) that the brain cells are becoming insensitive to insulin, like the rest of the body's cells in type 2 diabetes. The outcome of these discoveries is that new anti-diabetic drugs which help the cells of people with type 2 diabetes respond to insulin are now being tested in people with Alzheimer's disease who are not diabetic to find out if they can reduce the abnormalities in the brain. There are promising indications of memory and cognitive improvement in these people.



- **Head injury** – also know as “traumatic brain injury”, or TBI.
- **Strokes and “Ministrokes”**– the latter are very small hemorrhages in the brain that seemed not to have caused any symptoms when they occurred, but evidence that they did indeed occur is clearly visible when routine brain imaging is done at later times. It is now known that both strokes and TBI cause increases in enzymes called caspases, which then, through a series of biochemical steps, allow other enzymes called BACE to build up in the brain. This is bad news, because increased BACE activity is partly responsible for the excessive formation of A-beta in Alzheimer's disease.
- **High cholesterol levels**
- **High blood pressure**
- **Mild Cognitive Impairment (MCI)** – this important risk was mentioned earlier (“What is Alzheimer's disease?”). A diagnosis of MCI is commonly regarded as indicative of a high, but not certain, likelihood of developing the full-blown Alzheimer's disease within the following 10 years.
- **The post-menopausal state in women** – twice as many women get Alzheimer's disease than men. This is partly explained by their living longer than men on average, partly because women are more prone than men to get diabetes, itself a risk factor, but in large part because in post-menopausal women there is a decline of the important hormone estrogen.
- **Down's Syndrome** – almost all with this disorder who survive into their 40s or beyond will develop the abnormal brain changes that characterize the brain in Alzheimer's disease, but importantly, not all of these will actually develop dementia.
- **Chronic inflammatory conditions**, such as certain forms of arthritis.
- **A history of episodes of clinical depression**
- **Stress**
- **Lack of physical exercise**
- **Inadequate exercising of the brain** – in a twin study, the ones doing more intellectually demanding work were less likely to develop the disease than their identical twins.
- **Unhealthy eating habits**
- **Obesity**

- **Low levels of formal education**
- **Low socio-economic status**

There are also risk factors that are not so firmly established such as smoking, excessive drinking, and taking drugs of abuse. Researchers are still examining whether some people are at risk because their bodies have difficulties in handling foods containing the metals copper, iron, and aluminum, although most researchers no longer regard aluminum as a risk factor for Alzheimer's disease. Finally, some of the risk factors, particularly the last two listed above (low education and/or socio-economic status), may actually have been identified as such because persons in those categories are often people exposed to risk factors such as inadequate exercising of the brain and of the body.

Always remember, however, that exposure to any or even to all of the known risk factors does not mean that a person will get Alzheimer's disease. Equally one may have limited exposure to the known risk factors and yet still develop the disease.

How can we reduce the risk of developing Alzheimer's disease?

Only the genetic risk factors and aging are currently beyond our control. It's important to understand that what matters is not only how many risk factors a person might be exposed to, but as already mentioned, how efficiently the self-healing processes in his or her brain operate. It seems that the brain's ability to withstand risk factors and to preserve and even enhance its healing capacity can be enormously helped by adopting appropriate healthy lifestyles. These actually enhance the production in the brain of "growth factors" (more on these later), which promote the ability of brain cells to maintain connections with each other and make new connections. Recent discoveries suggest that healthy lifestyles may even help in the creation of new nerve cells, which is discussed later in the context of brain repair. The importance of lifestyle can be appreciated from studies of identical twins, who share the same genes. It turns out that about 60 per cent of the overall risk factor for Alzheimer's disease comes entirely from lifestyle and not genetic susceptibility. Healthy lifestyles are often effective in reducing the Alzheimer risk indirectly, by reducing specific risk factors such as stress and obesity. Of obvious benefit is the appropriate treatment of medical conditions such as diabetes, high cholesterol and high blood pressure levels.



Things that have been identified as helping reduce the risk of Alzheimer's disease, or to slow the disease progress once it has begun, include:

- **Healthy eating** – the focus here is on a Mediterranean type diet, and especially on eating anti-oxidant rich foods such as blueberries and raspberries, and dark green leafy vegetables such as spinach and collard greens. Also recommended by some are the anti-oxidants selenium and folic acid. Folic acid, also called folates, is also reputed to help ward off heart disease. It occurs in a wide variety of foods ranging from liver and fruits to whole wheat bread and lima beans, but like vitamin C is destroyed by cooking or processing. Reduced blood levels of both folate and vitamin B12 have been associated with increased levels of homocysteine in the blood and with increased incidence of dementia, but the benefits of B12 supplementation have not been satisfactorily established. Recently a beneficial effect of fruit and vegetable juices was reported (at least three glasses weekly) that appeared to be more related to the presence in the juices of antioxidants called polyphenols, rather than the presence of the antioxidant vitamins such as E or C (different anti-oxidants target different members of the "reactive oxygen species" category of substance described earlier). Moderate intake of red wine has also been promoted, particularly from French sources, as an approach to reducing the incidence of Alzheimer's disease. Similarly, certain spices used in curries, especially curcumin, have been implicated in the lower than average incidence of Alzheimer's disease in curry-eating populations, and research is actively underway to identify drugs that would mimic the active ingredients of the spices used. One important effect of curcumin



is its ability to bind to A-beta and thereby prevent the individual A-beta molecules from sticking together to form the toxic “oligomers” which are explained in the “Brain changes” section following. Finally, there is a new interest in increasing one’s intake of omega-3 fatty acids, found especially in cold water fish, flax and walnuts, after findings that these fatty acids were low in people with Alzheimer’s disease, and that in some studies (but not in all) their dietary supplementation improved cognitive functioning.

- **Aerobic exercising** – even the most modest levels are beneficial, such as a few daily walks up and down stairs. In one Canadian study people exercising three times a week were 40 per cent less likely to develop Alzheimer’s disease. Research indicates that exercise stimulates the production in the brain of the growth factors already mentioned, especially one known as BDNF, which both promote connectivity between nerve cells and help preserve their health. Also, exercising almost certainly helps maintain a good blood supply and therefore oxygen supply to the brain. This is particularly important because of the evidence that hypoxia, a reduced oxygen supply, of the brain promotes the production of the suspect protein beta amyloid, or A-beta.
- **Maintaining normal blood pressure**
- **Keeping cholesterol levels at normal levels**
- **An active social life** – including interactive and especially organized social leisure activities, for example playing

cards or group theatre-going. Loneliness in seniors has been linked to a higher risk for dementia, and clearly increased socialization would help here, including things like spending time with family.

- **Intellectual activity** – the use it or lose it principle, such as doing crossword puzzles, reading or playing chess. Interestingly, in a Swedish twins study, greater participation in intellectual activities was associated with lower risk for Alzheimer’s disease for women, but not for men.
- **Protecting your head** – especially by wearing safety helmets during recreation and sporting activities to reduce traumatic head injury.
- **Hormone replacement therapy (HRT)** – despite a recent large-scale clinical study on women which recommended discontinuation of HRT because it was both ineffective and had potentially dangerous side effects, a number of clinical researchers continue to regard it as worthy of further study, especially because of studies showing that estrogen treatment of post-menopausal women effectively reduced the incidence in them of Alzheimer’s disease. Animal studies are also pointing to the possibility that testosterone treatment could benefit men in this regard. Time will tell.

The accepted view today is that adopting a lifestyle that promotes a healthy brain, essentially much the same as one which promotes a healthy body, is the most effective way of reducing one’s chances of developing Alzheimer’s disease, and of slowing down the progress of the disease in those that have it. Adopting a lifestyle that ignores risk factors does not mean one will develop the disease, but it does increase the odds.

Four brain changes that occur with Alzheimer’s disease

The major unknown in Alzheimer research is exactly how the risk factors lead to the development of oxidative stress in the brain and to the production of the characteristic pathological changes, of which the most prominent are the loss of nerve cells, the appearance of plaques and tangles, and inflammation. Once these are produced, however, their threat to the brain is beginning to be well understood, leading to the rational design of drugs and the promotion of a healthy lifestyle, all with the aim of reducing that threat.

i) The plaques

These are made largely of the protein already mentioned, called beta amyloid, or A-beta, which is actually split off from a much larger protein molecule known as APP. Both APP and A-beta are present in normal brains, but their function is still under investigation. The key problem in Alzheimer's disease is that abnormally high amounts of A-beta accumulate in the brain, overwhelming the enzymes and other molecules whose job it is to clear it away. As well, the clearing away process itself appears to be defective. This applies even in the aging brain, in which at least two of the enzymes that help eliminate A-beta become progressively reduced whether Alzheimer's disease is present or not. It is now accepted that the real danger comes when the individual A-beta molecules clump together to form small toxic aggregates called oligomers. The continuing aggregation eventually leads to the formation of the amyloid plaques. However, the oligomers are so toxic that by the time the plaques appear the damage seen in the Alzheimer brain has already occurred.

ii) The tangles

The "neurofibrillary tangles", to give them their full name, are made of a protein called tau, which, like amyloid, occurs in normal nerve cells, but in Alzheimer's disease it becomes chemically altered and piles up as thread-like tangles, impairing tau's key roles in nerve cells. One of these roles is in nerve sprouting, an important feature of self-repair in the nervous system which is described later. Another tau role is in maintaining a kind of railway track system inside nerve cells that moves needed chemicals and tiny organelles up and down the nerve fibres between the cell body and the distant nerve endings. The cell body is the factory and powerhouse for the entire nerve cell. This transport system is essential for the cell to work and survive, and the tangles disrupt it and in a sense choke the cells to death. The first casualties of disrupted transport are the nerve endings, which contact the next cells in the circuit; these junctions are called synapses. They're vulnerable because they're so far away from their cell bodies, the source of their nutrients. Consequently the earliest signs of disturbed nerve cell function are seen at the synapses,

and in animal models of Alzheimer's disease it is here that researchers focus to see if future therapies are proving successful.

A controversy

Many researchers believe that the amyloid deposits not only make the nerve cells sick, but they somehow promote the development of tangles, and it is probably these that actually kill the nerve cells. In keeping with this "cascade hypothesis", when mice models of Alzheimer's disease were immunized against A-beta, not only the plaques but the tangles tended to disappear. Moreover tangles generally appear after the plaques have developed. In any event both plaques and tangles are definitely implicated in Alzheimer's disease. New research is suggesting that a very early event is the entry of the accumulating A-beta molecules into the nerve cells where the A-beta interacts with tau molecules that may be already altered, to form a deadly toxic product that is responsible for the earliest degenerative changes in the nerve cells and synapses.

But the situation is complicated. The brains of some normal elderly people have been found to have as many amyloid plaques as in Alzheimer brains, but there was no dementia! Nevertheless, most researchers still regard A-beta as the main threat, and still direct their efforts to eliminating it. This laudable and necessary attempt to cure the disease may not, however, be enough. To cure the person with the disease needs more, as will be seen later!

iii) Inflammation of the brain

Whenever and wherever the body suffers trauma, or is attacked by some kind of potentially threatening influence such as an infection or a toxin, it defends itself in part by mounting an "inflammatory response". This, which is actually an immune response, also occurs in the Alzheimer brain. Unfortunately the disease challenge is so great that the response becomes excessive, and instead of helping it actually worsens the situation. When the brain's immune cells (called microglia) become overactive they seem to overproduce substances that are normally protective, to a level which actually promotes death of cells. Moreover new results are suggesting that in Alzheimer's disease the very early

activation of these microglia actually helps trigger the changes in the tau protein that result in the formation of tangles.

iv) Shrinkage and degeneration of nerve cells

As nerve cells die and disappear that part of the brain shrinks. This process, which first begins in the part of the brain that deals with thinking and memory, is progressive, eventually affecting all parts of the brain, which consequently shrinks as a whole. The shrinkage is most marked, however, in the thinking and memory regions, and this is very readily seen by brain imaging.

Dr. Alzheimer noted and described three of the above pathological changes seen in the Alzheimer brain (i, ii, and iv). It's understandable that he missed number (iii), inflammation, since the recognition of immune cells in the brain and their functions had not yet entered medical science, nor had the concept and the importance of oxidative stress.

How is Alzheimer's disease diagnosed?

Although plaques and tangles are the distinguishing abnormal features that prove (in association with dementia, of course) the presence of Alzheimer's disease, these pathological appearances unfortunately have traditionally been able to be identified only post mortem. Actually this situation is beginning to change, as will be seen below, but generally speaking this is still true. Nevertheless it is not a particularly important item. In practice, the results of the tests doctors, along with their psychologist colleagues, make usually result in

a 90 to 95 per cent accurate diagnosis of Alzheimer's disease. A number of approaches assist them in their diagnosis. First they have to eliminate other known conditions that can cause or mimic dementia, such as Parkinson's disease, thyroid problems, depression, vitamin deficiencies, or excess of alcohol. They also make a routine examination of the general health of the person, including standard procedures such as blood pressure measurement and neurological testing (reflexes, muscle strength, speech, sensation, etc). And finally comes a battery of psychological and memory tests. An important one of these is the mini-mental state examination (MMSE), in which the person is presented with a series of questions designed to test a range of everyday mental skills. Another popular test is the mini-cog, which involves remembering the names of common objects, and drawing the hour and minute hands in a face of a clock to show times specified by the examiner.

Brain imaging

Sometimes doubts or concerns exist that the doctor might feel require further tests to be sure of the diagnosis. The person is then referred to a specialist clinic. Some of these use more sophisticated psychological approaches, and some will use brain imaging. Magnetic resonance imaging (MRI) and computed tomography (CT) give valuable information about the shape and volume of brain regions. The brains of people with Alzheimer's disease shrink significantly as the disease progresses (largely due to the loss of nerve cells), and shrinkage in specific regions of the brain may be an early sign of the disease. Positron emission tomography (PET) and functional MRI (fMRI) reveal how well cells in various brain regions are actively using the sugar or oxygen brought by the brain's blood supply, functions which significantly reduce in Alzheimer's disease. And finally, exciting new imaging techniques are emerging that address the problem of learning what's happening in regard to plaques during life rather than post mortem. Special tracer compounds, chemicals that show up in the imaging process, are injected into the blood circulation and thereby reach the brain. These chemicals attach to the A-beta proteins that form the plaques, which are then visualized without any surgery or exposure of the brain. One day this technique could become widely available, assisting not only in the diagnosis of Alzheimer's disease, but also helping to show whether treatments are working, since these treatments would be expected to significantly reduce the number of plaques.



Other diagnostic approaches

A revised diagnostic testing protocol has been recently proposed which includes imaging evidence for shrinkage of key brain regions, evidence of reduced glucose utilization in the brain, the presence in the cerebrospinal fluid (the CSF, the fluid which bathes the brain and spinal cord) of abnormal levels of A-beta, evidence of the existence of a genetic mutation for Alzheimer's disease within the immediate family, and of course indications of dementia. Discussion continues on whether this newly proposed set of criteria should become the universal standard.

It was recently reported that the steady weight loss normally associated with aging doubles in the year before even the mildest Alzheimer-like symptoms become evident. This in itself would make only a minor contribution to diagnosis, but it does support the quite common belief that Alzheimer's disease might be affecting body functions earlier than brain ones. Findings like this, if true, support the endeavors of researchers who are continually looking at persons in the earliest stages of Alzheimer's disease for unusual changes in easily examined tissues like the skin, blood, CSF, and the urine. The aim is to find simple laboratory tests for early diagnosis, and some success is occurring here.

Drug treatments for Alzheimer's disease

i) Aricept™ (donepezil), Exelon™ (rivastigmine) and Reminyl™ (galantamine)

These drugs are cholinesterase inhibitors. They help preserve the ability of sick nerve endings to transmit the nerve messages to the next cell in the chain. The first of these drugs appeared in 1986, but wasn't consistently effective until ten years later when along came the new generation of cholinesterase inhibitors, and their success was rapidly recognized.

How they work makes a fascinating story. Nerve messages, or impulses, travel along nerve fibres by an electrical mechanism, but the electricity is inadequate to cross the junctions between the nerve and the next cell. Nature invented a mechanism to deal with this problem: each arriving impulse releases a tiny blip of a chemical called a neurotransmitter, which diffuses very rapidly across the junction to stimulate the next cell. For Alzheimer's disease the most important neurotransmitter is acetylcholine, the one used by

the nerve cells in the thinking and memory-making parts of the brain. After the acetylcholine has carried the message across the junction it's critical that it be eliminated immediately, otherwise it would keep on stimulating the downstream cell. This could be disastrous, leading to seizures for example. Nature dealt with this potential danger by ensuring that the acetylcholine is destroyed immediately after it's delivered the message, and this is done by an enzyme called cholinesterase.

Now, in Alzheimer's disease the blip of acetylcholine that is released by each arriving nerve impulse gets progressively smaller and smaller as the nerve endings get sicker and sicker, eventually becoming too small to transmit the message across the junction. Cholinesterase inhibitors prevent cholinesterase from destroying acetylcholine, and thus what little acetylcholine is released is preserved, building up to levels high enough to get the message across to the next cell. And it works! However, eventually the sick nerve endings begin to degenerate and withdraw from the junctions and messages can no longer be transferred across them. To reach this point takes usually from two to three years (but sometimes much longer), which is why cholinesterase inhibitors usually work best in the short term.

Remarkably, however, in some instances cholinesterase inhibitors seem to have been effective for as long as 8 to 10 years, and new research (including Canadian studies) is finding that donepezil can continue to have beneficial effects in improving symptoms even in severe Alzheimer's disease. This finding fits in with other evidence that another action of cholinesterase inhibitors is somehow to protect nerve cells from damage by oxidative stress. It has to be acknowledged, though, that there is an unexplained variation among individuals as to how well they respond to cholinesterase inhibitors, and how badly they are affected by the side effects, which include diarrhea, insomnia, nausea, infection and bladder problems. To avoid side effects one drug company is trying a new method. The drug (Exelon™) is not swallowed but is contained in a skin patch from which it is absorbed directly into the body. The usual problem of patch administration is knowing the exact dosage being taken in, but this appears to have been



solved, and so this approach offers substantial promise for eliminating the side effects of cholinesterase inhibitors.

The consensus remains that, though not a cure, cholinesterase inhibitors are of benefit to at least a significant proportion of those with diagnosed Alzheimer's disease, and a promising development discussed later is the use of cholinesterase inhibitors in combination with other drugs like Ebixa®.

ii) Ebixa® (memantine hydrochloride)

This story has to start by talking about another neurotransmitter called glutamate. Unlike acetylcholine, glutamate is not destroyed by an enzyme after doing its job of conveying the message across the junctions between nerve cells. Instead it's taken back up into the nerve endings from which it was released, or in other words, it's recycled. This uptake requires that the glutamate combines first with special receiving molecules on the nerve endings called glutamate receptors (known as NMDA receptors). However, there's a twist to the story here. All the cells of the body contain a lot of glutamate because it has important metabolic roles aside from being a neurotransmitter. When cells get sick, especially nerve cells, glutamate leaks out, and its concentrations outside the sick nerve cells can be so high that the increased amount that's taken back by way of the glutamate receptors is toxic, and indeed quite deadly. This is one of the reasons nerve cells die in Alzheimer's disease – their sickness could be initially mild, but the massive glutamate leakage and re-uptake multiplies the threat.

Memantine acts by blocking the glutamate receptors and preventing the re-uptake of the glutamate into the nerve endings. The beauty of this approach is that enough glutamate gets back into the sick nerve endings to be used as a transmitter, but the massive uptake that would be toxic is prevented. Since the glutamate threat develops somewhat late in Alzheimer's disease, memantine stands as one treatment that can be effective at moderate to advanced stages of the disease. And there is better news: ongoing research is finding that combining cholinesterase inhibitors together with memantine seems to greatly improve the outcome, more than predicted from the sum of the effects of either drug alone. This combination therapy seems likely to become an exciting therapeutic approach in the future.

What other leads are being followed that could lead to earlier diagnosis or new treatments?

i) Vaccines

There are promising developments here. Vaccines became a real possibility when animal models of Alzheimer's disease were created (that is, genetic engineering was used to get the genes for familial Alzheimer's disease into mice). The brains of these mice develop amyloid plaques and the mice are memory-impaired.

Researchers then designed a modified A-beta which, when it was injected into the mice, induced their immune systems to make antibodies against it. Because the modified A-beta was so like the normal A-beta, the antibodies they generated also worked against the A-beta already in the brain, and the result was a significant reduction of the plaques and an improvement in the cognitive abilities of the mice. Human trials were rapidly undertaken, only to be dramatically stopped in 2002 when some of the participants developed alarming brain inflammation (this didn't happen with the mice).

So where do we stand? Well, new modified A-beta vaccines are being vigorously sought – and found – that are predicted not to cause brain inflammation. Also, new mouse models are now being produced with neurofibrillary tangles in the brain cells, and anti-tangle

antibodies are being made and tested. In one new approach the vaccine is given as a nasal spray, which is claimed to stimulate the brain's immune cells (the microglia), which then will mop up the excess A-beta molecules. In another approach, instead of giving substances which will stimulate the production of antibodies (active immunization), already manufactured antibodies are provided directly (made either in animals or cultures of living cells). This approach, called passive immunization, bypasses the immune system of the body, hopefully thereby reducing the chances of triggering adverse inflammation of the brain. Finally a new experimental vaccine has been created which targets neither A-beta nor the "tau" protein of the tangles, but instead it targets one of the key enzymes involved in splitting the toxic A-beta from its big parent protein. While much remains to be found out, a number of these exciting animal studies have already been extended to human clinical trials, and the early news gives definite hope that within five to seven years, there could well be a vaccination therapy that could revolutionize the treatment of Alzheimer's disease.

ii) MCI

Some important developments relate to MCI, a condition that is being increasingly found in early middle-aged and even young adults. MCI is clearly an important risk factor for the disease. Brain imaging is showing that abnormal changes almost certainly exist in the brain even before MCI is diagnosed, and indeed even in some totally non-MCI people's brains that later developed symptoms of Alzheimer's disease. Some researchers believe that plaques may begin to appear as early as 5 to 10 years prior to any signs of dementia. Imaging approaches, added to psychological testing, should make it possible both to pick out the most at-risk MCI individuals, and to assist enormously in the early diagnosis of Alzheimer's disease. This is important: earlier diagnosis means earlier treatment, and the sooner a therapy is started the better. Many (but not all) clinicians are now recommending that cholinesterase inhibitors be given to people diagnosed with MCI without waiting for signs of Alzheimer's disease to appear.

iii) Statins

These cholesterol-reducing agents are being investigated because the incidence of Alzheimer's disease appeared to be less for people using these drugs to lower their cholesterol levels. At first it was assumed that the benefit of these statins came from their ability to reduce the incidence of cardiovascular disease (diseases affecting the heart or blood vessels), which is a risk factor for Alzheimer's disease. However, we now know that statins also reduce the production of A-beta from APP, so here is another promising future treatment strategy. Moreover, since cholesterol is a key component of the membranes that enclose nerve cells, abnormal cholesterol levels could seriously alter cell membranes, and the responses of nerve cells to substances such as growth factors, hormones and of course drugs. Keeping cholesterol from rising above normal levels is clearly very important.

iv) Alzheimer's disease and diabetes

As discussed in the section on Risk Factors, research on people with Alzheimer's disease and on animal models of the disease is showing that, even when diabetes in the conventional sense is absent, anti-diabetic drugs called "glitazones" can help maintain brain function and, seen in the animal studies and assumed to occur also in people, reduce the development of brain plaques. This approach is supported by the observation that insulin administered through the nasal passage, which can get preferentially to the brain without going through all the rest of the body, improved memory and cognition in some people – a promise of future therapeutic measures.

v) Anti-inflammatory agents such as aspirin and other NSAIDs (nonsteroidal anti-inflammatory drugs)

Although not yet proven, there is intriguing evidence that people routinely taking anti-inflammatory agents for rheumatic and other conditions are at a decreased risk of getting Alzheimer's disease, and this lead is being followed up. Cannabinoids (cannabis-derived substances) have also been claimed to have anti-inflammatory and other benefits in Alzheimer's disease, but at present the potential dangers associated with their numerous actions in the nervous system make their use problematical.

vi) Other drug therapies

Flurizan™ is an example of a new class of drugs currently in clinical trials. Flurizan and other “secretase inhibitors” work by blocking the process that splits off A-beta from its big parent molecule, APP. This helps to stop the dangerous accumulation of A-beta in the brain. Other drugs, including cyclohexanehexol, a new agent discovered by Toronto researchers, interact with the A-beta molecules as they form, and prevent them from sticking together in small aggregates - aggregates that poison nerve cells and eventually deposit as solid “plaques”, but by the time they form most of the damage is already done. Alzhemed™ is another such drug, but its initial promise was not supported in expanded clinical trials, and it has now been discontinued. Other treatments aim at encouraging the mopping up of the A-beta before it reaches threatening levels. Ubiquitin is a naturally-occurring chemical in the brain that helps in this mopping up action, but its levels are reduced in Alzheimer brains. When mice with Alzheimer's disease were given drugs that increased their ubiquitin levels, their brain function improved even when the amyloid plaques persisted. Presumably this was because the drug prevented the very small toxic aggregates of amyloid from developing. Iron, zinc and copper, which are virtually impossible to avoid in normal diets, are needed for the A-beta molecules to clump to form the toxic oligomers, and they have been suggested as risk factors for Alzheimer's disease in certain individuals. This possibility is being tested in trials of a drug called Clioquinol that helps remove the suspect metals from the body. Definitive results are not yet in from these studies. Finally ginkgo biloba, a herbal supplement purported to improve memory, is in clinical trials to see if it affects the onset or severity of Alzheimer's disease.

vii) Early diagnosis by measuring chemical levels in tissues outside the brain

It has long been hoped that biological markers for Alzheimer's disease would appear in various tissues that could be more easily accessed and studied than the brain itself. New findings are offering hope that early diagnosis may become possible through such biological markers. Recent reports described two such

in the skin of people with Alzheimer's disease, firstly an abnormal inflammatory chemical response that is easy to detect, and secondly, the presence of abnormal levels of a number of proteins. Other studies on people with Alzheimer's disease are revealing alteration in their CSF levels of A-beta and tau, the two proteins most implicated in Alzheimer's disease. The search goes on for biological markers of Alzheimer's disease, and scientists are hopeful.

viii) Making new nerve cells from stem cells:

Stem cells and their promise

Researchers are very excited at the prospect of replacing lost nerve cells in Alzheimer brains by using special cells known as stem cells. These are immature cells that have not yet developed to the stage when they show a recognizable mature identity, that is, one that would label them as nerve cells, heart cells, liver cells, and so on. Stem cells occur naturally in most of the body's tissues, such as bone marrow, skin, and also the brain, and apparently are used as a source of replacement cells to be recruited whenever tissue degeneration occurs due to disease or trauma (part of the body's natural repair strategy). There is evidence that the repair function offered by resident stem cells converting into nerve cells can happen spontaneously after traumatic brain injury, and even in neurodegenerative conditions like Alzheimer's disease. The aim of Alzheimer researchers is to encourage this process, but even more so to obtain a reliable and abundant “outside” source of stem cells and then to get them into the regions of the brain where nerve cell degeneration has occurred. What are the chances of achieving this aim?

Stem cells are multipotent, or pluripotent, meaning that under appropriate conditions any stem cell can transform into any particular adult cell types. This transformation is brought about in the body, and also in the experiments done by researchers, by exposing the stem cells to ‘trophic’ substances, also called growth factors. These factors are natural nourishing molecules made especially in the embryo to guide the development of stem cells along the road to becoming specific mature cells, but trophic factors are also made continuously throughout life to help maintain the health of virtually all the cells in the adult, including nerve cells.

One of the most important of these trophic molecules, the first such to be discovered actually, is called Nerve Growth Factor, or NGF for short. NGF is needed especially to keep the brain cells involved in memory and thinking alive and well, and therefore, as explained following, is of special interest as a potential treatment in Alzheimer's disease. The stem cell replacement approach is being very actively studied in experimental animals, and in some countries preliminary tests have begun in people with Alzheimer's disease, with ambiguous results.

Where will the stem cells come from?

A persisting problem has been how to obtain the substantial numbers of stem cells needed for their study, and will certainly be needed if they're going to replace cells lost in diseases like Alzheimer's disease. In theory this can be solved, once a source of stem cells has been established, by transferring the cells to a special chamber containing an appropriate nutrient broth in which they are "cultured", i.e. allowed to grow and divide, which they will do readily and apparently indefinitely. The most popular source of stem cells to date has been embryos or fetuses, in which stem cells are abundant, and also from the amniotic fluid that surrounds the fetus. There are, of course, ethical considerations in obtaining stem cells from human fetuses, and Canada, in common with many other countries, has important limitations on stem cell research in this regard. However, two recent research reports have cast an entirely new light on the situation. Using a 'retrovirus' as an infecting agent, certain molecules known as 'transcription' factors were introduced into fully developed human skin cells. Transcription factors regulate (or "activate") genes. Using the virus, the researchers effectively shuttled up to four transcription factors into mature skin cells. These factors were already known to be highly active in stem cells, but not in adult cells. The effect of these transcription factors was to activate genes that converted the adult skin cells back into an earlier and more primitive state, into cells in fact that closely resembled normal embryo-derived stem cells. In the jargon, the skin cells were 'reprogrammed'; their original adult character was lost, and instead they looked and behaved like normal immature stem cells. The excitement

generated by these two reports was not just because of the discovery of how to transform normal adult cells into stem cells, but because of the implication that stem cells could now be obtained without the involvement of human fetuses. So the question becomes – how near are we to using stem cells reliably and safely as replacement nerve cells in people with Alzheimer's disease?

Pluses and minuses of stem cells as potential replacement cells:

Some big pluses – When any foreign tissue or cells are transplanted into a person, their immune system immediately starts to work to get rid of what it views as potentially harmful invaders. This is called 'rejection', and to prevent it the host recipient has to be given immune-suppressants. This is hazardous, because now the body is being deprived of its most important defense against dangerous threats such as infection and the development of tumors. A wonderful advantage of using skin as a source of stem cells is the possibility of using the skin of the person him or herself, thereby allowing for a replacement cell strategy without the complication of rejection. This reasoning is a powerful plus in favor of creating a skin-derived stem cell industry. Moreover, because of the 'immortality' of stem cells already referred to, once they are obtained in a laboratory setting they constitute a persisting source of continuously dividing stem cells that needs no renewal.



Are there drawbacks? Indeed yes - there always have been problems associated with the idea of a stem cell therapy whatever the source of the cells.

- i) the genetic make-up of the stem cells created using retroviral infection of adult skin cells described in the new reports mentioned above was not identical to that of conventional embryonic stem cells. It's not yet known how abnormal the consequences of these genetic differences might be. One major concern is that the use of a retrovirus might introduce the potential for initiating tumors in the host body, or of causing undesirable genetic mutations in neighboring cells. Moreover, reprogrammed adult skin cells might still contain DNA abnormalities caused by earlier exposure to sunlight or environmental toxins, hazards that could carry over to the newly created stem cell population.
- ii) There is other evidence that laboratory cultured stem cells are not guaranteed to convert into totally normal adult cells. In some earlier Canadian studies stem cells (actually obtained from adult skin) were transformed into what looked like perfectly normal nerve cells, but it turned out that some critically important mechanisms required for the cells to produce nerve impulses (messages) were missing--an important defect by any standards!
- iii) To promote useful functions any nerve cells implanted into the brain have to become correctly integrated into the existing neuronal circuitry. The implanted material has to be positioned at the right anatomical sites, the new nerve cells have to be recognized by other nerve cells as appropriate targets with which to make new connections, and they themselves have to grow out nerve fibres that will make connections with the correct receiving nerve cells.

What are the chances of these circuitry needs being successfully accomplished?

Daunting though these problems may seem, there is an unexpected kind of evidence which supports the possibility of implanted nerve cells becoming appropriately integrated into the host nervous system.

It seems that “cues” exist, even in adult nervous systems, which help guide newly-growing nerve fibres to correct destinations. Apparently some of the mechanisms that operate during early development, to ensure that the correct connectivity is achieved, survive into adulthood. That such mechanisms were once there is clear. Were they absent, and supposing that trial and error were ultimately responsible for ending up with the correct connectivity in the brain, this would take literally hundreds of years to achieve rather than the months of fetal brain development. So, provided that neuroscientists are able to implant stem cells, or stem cells already transformed into adult nerve cells, into the required brain locations, it could be that enough new connectivity would spontaneously develop to maintain or restore functions threatened by disease or trauma. In the case of Alzheimer's disease, the brain regions involved in memory and cognitive functions would be the prime ones to receive such implantations.

How long before we have a viable stem cell replacement therapy? The best guess of this writer is decades at the very least. This is not to deny the potential of such therapy, which offers a direct solution to the loss of nerve cells in the brain. But while we await this desirable result, it's encouraging to know about the other promising treatments that are on the horizon.

ix) **Promoting brain repair:** The special importance of stem cell studies and others now to be mentioned is that they address the problem of brain repair. If the brain functions that are lost in Alzheimer's disease are to be restored, the brain damage must eventually be reversed. Even when a truly successful treatment for Alzheimer's disease appears, i.e. one that actually stops the disease in its tracks so that there's no further brain degeneration, there will still be the need to deal with the damage that's already happened. We have to cure the person as well as the disease! Of great importance here are the growth factors such as NGF described earlier. Growth factors also stimulate nerve cells to sprout new branches and make new connections to make up for those lost as neighbouring nerve cells die. This compensatory nerve sprouting helps recovery after stroke and brain trauma, for example. Unfortunately it doesn't occur so readily in aging, and it is also reduced by some of the known risk factors for Alzheimer's disease. Scientists are now

implanting genetically engineered cells that make NGF into the brains of animal models of Alzheimer's disease, and in one study NGF-producing cells were implanted directly into the brains of people with Alzheimer's disease. Initial results show promise both for keeping nerve cells from dying and in improving cognition and memory.

It is certain that the three approaches, delivery of growth factors, delivery of stem cells, and mobilizing stem cells already resident in the brain, will one day pay off as a way of reversing the damage caused by Alzheimer's disease. However, all of this will take quite a few years. Another more immediate and quite different way of promoting brain repair is described in the following section.

A proposal: caregiving could be promoting brain repair

Nerve sprouting from surviving nerve cells is a key feature of repair in the diseased or damaged nervous system. The new sprouts make connections with other surviving nerve cells, compensating for the connections lost when nerve cells died. Nerve sprouting is induced by growth factors among which NGF is very important. However, there is another way to induce nerve sprouting; this is by initiating impulses (nerve messages) in the nerve cells. Experimentally this driving, as it's called, is done either by electrically stimulating the nerve cells, or by increasing the sensory input, that is by providing increased sensory stimulation such as light, touch, sound, and so on. Now in the parts of the brain that control feeling and thinking, the input that matters most is that from the social environment – from people talking and touching or caressing, physically and emotionally interacting with the individual. This means that the more of this social stimulation a person with Alzheimer's disease gets, the more likely it is that their surviving brain cells will be induced to sprout and restore lost connections. Not only that, but research is showing that in mouse models of Alzheimer's disease, environmental enrichment, which is a form of increased social stimulation, actually reduces the levels of A-beta and the amyloid deposits. Also, in normal mice, environmental enrichment promoted sprouting and increased connectivity between brain cells.

The caregiver, family member or anyone else involved with the person with Alzheimer's disease has a critical role

here. We should never be put off by absence of immediate response because nerve sprouting and the subsequent making of connections with other nerve cells can take many months. Now this proposal has obviously not been proven experimentally in humans, but a lot of animal research would support it, and anecdotal accounts from caregivers support it too. The emotional benefits of maintaining contact between people with Alzheimer's disease and their caregivers and family members can only be guessed at, but the bottom line is – keep trying to communicate, keep talking, and keep on showing affection like holding and caressing (without overdoing it of course, which could cause distress to both sides). The thing to avoid at all costs is social isolation.

Animal studies offer hope that lost long-term memories may be recoverable

In this work two genes were studied in mice. One gene, when activated by appropriate drugs, caused nerve cells to die just as in Alzheimer's disease, and as in Alzheimer's disease, long-term memory was lost. The first, truly exciting result was that when put into an enriched environment, the long-term memory eventually reappeared, despite the loss of nerve cells. Thus the memories were there, but couldn't be accessed until new connections were made by the surviving cells. So the message in the preceding section gains more support: socialization and stimulation can eventually help restore memory in a damaged brain.

The second gene the researchers studied is involved in the formation of long-term memories (probably by sprouting new connections). Unexpectedly, a protein that occurs normally in the body was found to suppress this gene, so interfering with long-term memory production. The researchers were able to oppose the action of this suppressor protein with another drug, and in these mice long-term memory formation was facilitated, even in brain-damaged animals.

Now all this is a long way from the human situation, but the message is critically important. Lost memories may not have disappeared forever. Even after nerve cells have died, the recovery of these memories may still be possible, provided new connectivity among nerve cells can be achieved. And this is possible, both by environmental stimulation, and one day by drug treatments.

The Next Ten Years

These could be even more exciting than the last decade. Let's look at some of the developments that seem most likely to pay off within ten years. Clinical trials (many already begun and some well advanced) will test the following, and hopefully within the next five to seven years the most promising of them will be approved for people with Alzheimer's disease:

1. Drugs that block the enzymes that split off the toxic A-beta from APP (secretases inhibitors).
2. Drugs that prevent the threatening clumping together of newly formed A-beta molecules.
3. Drugs (like Noprilysin) that help clear away the accumulating A-beta molecules before they begin clumping together.
4. "Neuroprotective" drugs (like the growth factors) that increase the ability of threatened nerve cells to stay alive.
5. Drugs that will prevent the chemical modification of tau protein, and so prevent tangles.
6. New vaccines that will eliminate both the production and the accumulation of amyloid (A-beta) but not have the dangerous side effects of the first vaccines.
7. New vaccines that will eliminate tangles.
8. Improved techniques to implant genetically engineered living cells into the brain for delivery of growth factors and other drugs to counteract the development of plaques and tangles.
9. New anti-diabetic drugs that will correct glucose metabolism in the brains of people with Alzheimer's disease.
10. New drug delivery techniques which will ensure that drugs get to the regions of the brain where they are needed.
11. Improved availability of non-invasive imaging techniques that will reveal plaques and tangles even before dementia develops. These techniques would use special chemicals injected into the blood, that reach the brain and attach to plaques, and are visualized by imaging, so facilitating early diagnosis and revealing whether treatment strategies are reducing the brain abnormalities.
12. New biological markers for Alzheimer's disease that can be measured in the blood, in the CSF, in urine, and in the skin, to help in early diagnosis, and in evaluation of treatment therapies.
13. Early diagnosis based on the pattern of brain waves (EEG).
14. New cognitive training regimens that will help slow down the decline in brain functioning without the use of drugs.
15. Delivery of therapeutic agents via the nose, in some instances associated with harmless viruses called "phages".



Where does the Alzheimer Society come in?

Canadian scientists rank among the top Alzheimer scientists in the world. To support these scientists, the Alzheimer Society is a leading funder of Alzheimer research and research training in Canada. In 2007, the Society (with our partners) funded 22 new grants and training awards, amounting to \$2 million. The funding for the research program comes from provincial and local Alzheimer Societies across Canada, and from the generosity of individuals and corporations. The Alzheimer Society of Canada (ASC) administers the research program. The research applications received for the annual competition are reviewed through an extensive peer review process, and the funding is divided equally between the biomedical and the social/psychological fields. ASC seeks out partnerships to enhance the impact of its research funding. Our current partners include:

- Provincial Alzheimer Societies and local Chapters across Canada
- Canadian Institutes of Health Research (CIHR)
- Canadian Nurses Foundation (CNF)
- Pfizer Canada Inc.
- Institute of Aging (CIHR)
- Institute of Gender and Health (CIHR)
- Fonds de la recherche en santé du Québec (FRSQ)
- Alzheimer Society Of Saskatchewan (supports Young Investigator Grants)

The Alzheimer Society Research Program supports biomedical research projects in essentially all the areas discussed in this Research Report.

While Canadian scientists rank among the top Alzheimer scientists in the world, the fact remains that there is currently no cure for Alzheimer's disease. Research remains the key to finding a cure, and if a cure is to be found, Alzheimer research must be made a higher priority in Canada, and more funding must be given in support of Canada's world class researchers.

This report focuses on biomedical advancements. A companion report is in development that will address the equally important Social/Psychological research. This companion report will be available in 2008.

Alzheimer Society

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