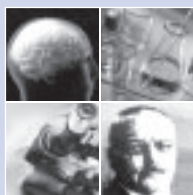


1906-2006 ALZHEIMER DISEASE



# 100

YEARS OF DISCOVERY

A Report on Alzheimer Disease  
and Current Research  
*For the non-specialist*

October 2005

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

Alzheimer *Society*



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### *Introduction*

For the past few years, Dr. Jack Diamond has been making presentations on Alzheimer Disease research for Alzheimer Societies across the country. From these presentations, A Report on Alzheimer Disease and Current Research has been created. This report is intended to describe current Alzheimer research in a non-technical way. It provides a description of the key areas of Alzheimer research currently under investigation and of the progress being made in each area. Due to the rapid changes that occur in the field of Alzheimer research, this report will be updated periodically.

### *Dr. Jack Diamond*



Dr. Diamond is the Scientific Director of the Alzheimer Society of Canada. He was formerly Associate Director for Scientific Affairs at the Montreal Neurological Institute at McGill University, and was the founding Chair of the original Department of Neurosciences when the new medical school was established at McMaster University in Hamilton, Ontario. Dr. Diamond is also Professor Emeritus in the Department of Psychiatry and Behavioral Neurosciences at McMaster University, where he continues to run his laboratory research program with a special focus on diabetic neuropathy and on the apoE4 risk factor for Alzheimer Disease. Prior to joining the Alzheimer Society of Canada, Dr. Diamond also served as a volunteer Scientific Committee reviewer and conference speaker for the ALS Society of Canada and the Spinal Cord Society.

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. His most recent publications appeared in the *Journal of Neuroscience* and in *Molecular and Cellular Neuroscience*. He is currently preparing a paper that will help clarify the role of apoE in the nervous system, and another that introduces a new animal model for the investigation of autonomic diabetic neuropathy.

### *The Alzheimer Society*

The Alzheimer Society is a nationwide, not-for-profit health organization dedicated to helping people affected by Alzheimer 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.

## *Table of Contents*

What is Alzheimer Disease? .....	1
How is Alzheimer Disease diagnosed? .....	2
What exactly are “risk factors”, and how far are they responsible for Alzheimer Disease? .....	2
How can we reduce the risk factors? .....	3
Biomedical Research .....	4-8
“Plaques and tangles”: what are they, why are they dangerous, and can they be treated?.....	4
How do drugs like Aricept™, Exelon™, and Reminyl™ work, and why only in the early stages of the disease? .....	5
What is Ebixa® and what is its promise?.....	6
Where does vaccination against Alzheimer Disease stand? .....	6
What other leads are being followed that could lead to earlier diagnosis or new treatments? .....	7
MCI .....	7
Statins .....	7
Anti-inflammatory agents.....	7
Other Therapeutics Remedies.....	7
Stem cells.....	7
Promoting brain repair .....	8
Social/Psychological Research .....	8-10
Caregiving and quality of life research.....	8
An exciting proposal: caregiving could be promoting brain repair .....	10
The Next Ten Years .....	11
The Researchers .....	11
Where does the Alzheimer Society come in? .....	12

**Alzheimer Society**



## *What is Alzheimer Disease?*

Alzheimer Disease is the most widespread of a large category of disorders known clinically as “dementias”.

The main features of dementia are a progressive deterioration of thinking (cognitive impairment) and of memory. In Alzheimer Disease there can also be behavioural changes such as agitation, aggression, and an inability to find the way even in familiar surroundings. Currently, an estimated 280,000 Canadians over 65 have Alzheimer Disease and more than half a million Canadians will have the disease by 2031.

While there is no specific known cause of the disease, it seems likely that Alzheimer Disease develops as explained in the following sections.

## *How is Alzheimer Disease diagnosed?*

Our awareness of the disease today stems from the observations of Dr. Alois Alzheimer himself in 1906, with his special study of a female patient with dementia of unknown origin. After the patient died, Dr. Alzheimer examined brain tissue in the microscope, and observed the “plaques and tangles” (described on page 4) now accepted as the hallmark traits of the disease named after him. If these distinguishing pathological (abnormal) features are there it proves Alzheimer Disease, but of course this can only be done post mortem. During life, doctors start by eliminating other known diseases that can cause dementia (Parkinson’s disease is one such). After that comes a battery of psychological and memory tests which are usually accurate in allowing a diagnosis of Alzheimer Disease to be made. However, brain imaging techniques such as Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) are becoming increasingly utilized to increase the accuracy of diagnosis even more. In one very promising approach, a harmless radioactive chemical (a molecular “probe” or “marker”) is injected into the blood stream that eventually get into the brain, where it attaches to tangles or plaques depending on the marker used. The plaques or tangles are thereby “labeled”, and since they can then be visualized in the imaging system, the clinician can get a measure of just how many of them there are. A successful anti-plaque treatment, for example, would then be seen to have reduced the numbers of plaques when the imaging was repeated at a later time, and hopefully this would be supported by results from psychological testing of the same person. Genetic testing for the presence of the “apoE4” gene, an important risk factor for Alzheimer Disease, is also contributing to the accuracy and rapidity of diagnosis in some countries, although genetic testing is not yet accepted as a routine procedure in Canada.



## *What exactly are “risk factors”, and how far are they responsible for Alzheimer Disease?*

Risk factors are characteristics that contribute to the likelihood of getting the disease. It’s often stated that we don’t know what causes Alzheimer Disease, but many are coming to the conclusion that in a sense we do know. All the organs of the body, including the brain, have built-in self-repair mechanisms. Alzheimer Disease appears to develop when the combined effects of the known and still to be identified 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. Researchers are studying ways to enhance these repair mechanisms. What we are still figuring out is how the risk factors exert their harmful influence. The biggest, indeed the obligatory, risk factor is aging, probably because the brain’s self-repair mechanisms deteriorate with age. The deterioration occurs at different rates in different people (perhaps this explains why some people are more susceptible to getting Alzheimer Disease than others). Whatever the risk factors, Alzheimer Disease never sets in until some minimum adult age is reached.

The age factor is particularly evident when it comes to the genetic risk factors. The genes associated with Familial Alzheimer Disease, which comprises about 7% of the Alzheimer population, are inherited, and they confer an enormous family susceptibility to Alzheimer Disease. Another gene, the apoE4 gene, is a risk factor in both the familial and the common “sporadic” Alzheimer Disease. Nevertheless, although these and other similarly threatening genes are there from birth, the carriers of them don’t get Alzheimer Disease until the brain has reached a certain critical age, significantly younger for familial than for sporadic Alzheimer Disease, but still well into adulthood. The age requirement applies also to all the other more general risk factors, which also become more threatening as the person ages. These risk factors include diabetes, previous strokes\* and head injury, previous episodes of depression, high cholesterol levels, high blood pressure, the post-menopausal state in women (twice as many women get Alzheimer Disease than men, though this is partly explained simply by their living longer than men on average), family history, Down Syndrome, and Mild

2 \* The vascular abnormalities in the brain which underlie Vascular Dementia (a dementia which closely resembles Alzheimer Disease) are sometimes found in people who never suffered a stroke, and are then called “silent strokes”. When these recur, however, they can lead to full Vascular Dementia but also to Alzheimer Disease, so silent strokes are also risk factors for both conditions.

Cognitive Impairment (MCI) (see page 7). There are also risk factors that are not so firmly established such as smoking, lack of exercise, low levels of education or intellectual functioning, low socio-economic status, and poor nutritional status. 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.

### *How can we reduce the risk factors?*

It's important to understand at the outset 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. Many of the risk factors for Alzheimer Disease, like the apoE4 gene, apply to other diseases as well. However, only the genetic risk factors and aging are beyond our control (but see the "aging" section that follows). Most of the others can be reduced by adopting healthy lifestyles such as exercising, not smoking, healthy dietary habits, and possibly taking dietary supplements such as vitamins, folic acid, omega-3 fatty acids and selenium (the "anti-oxidant" character of vitamins C and E used in combination does seem to have significantly reduced the incidence of Alzheimer Disease in one good study, although vitamin E supplementation has recently been reported as a potential health hazard). The importance of lifestyle in general can be appreciated from identical twin studies; although the twins share the same genes, when one twin gets the disease there is only a 40% chance that the other will also. This means that 60% of the risk factor of twins, and presumably all individuals, is related to specific lifestyle and not to genetic susceptibility. In another twin study the ones doing more complex work were less likely to develop the disease than their other twin. This fits in with the indications that increased intellectual activity may be beneficial (the "use it or lose it" principle). Keeping cholesterol levels from rising to above normal levels appears to reduce the risk generally, and may even reduce the special risk of the apoE4 gene. Researchers are also studying the role, if any, that hormone replacement therapy (HRT) may play in Alzheimer Disease. A recent large-scale clinical study on women recommended discontinuation of HRT as being both ineffective and having potentially dangerous side effects. However a number of clinical researchers continue to regard it as worthy of further study. Time will tell!



**Aging:** At first sight this key risk factor would appear to be the one that we can do least about. Surprisingly, 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, and there is a genuine feeling 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, but instituting an equivalent life-long CR in humans is just not possible (who would start their baby on a CR regimen and keep them on it for life?). However, the fact that body-aging can be influenced at all is a very important stimulus to scientific research on aging. Everybody knows that some older people seem to have remarkably young brains, and everybody knows the expression "he (or she) is old before their time". The point here is that from the perspective of Alzheimer Disease it is not chronological age that matters but brain age, something we can easily recognize but so far cannot control. Perhaps, as already mentioned above, it is the efficiency of the brain's repair mechanisms that matters, and how rapidly these are affected during aging. Scientists are well on their way to understanding these self-repair mechanisms, and are looking at ways to activate them when they seem to be "switching off" as in aging (see "An exciting proposal..." on page 10).

## Biomedical Research

### *“Plaques and tangles”: what are they, why are they dangerous, and can they be treated?*

Four important changes occur in the brains of people with Alzheimer Disease:

(i) *Here and there many of the nerve cells start to shrink, eventually disappearing (they degenerate).* This process, which begins in the part of the brain that deals with thinking and memory, is progressive, affecting all parts of the brain, which consequently shrinks. This is very readily seen by brain imaging. Every nerve cell has a relatively long nerve fibre which carries the nerve messages (the “impulses”) to other nerve cells. The distant endings of these nerve fibres suffer first when nerve cells become sick, simply because they’re so far away from the source of their metabolic needs, the nerve cell “body” (the cell body is the factory and power house for the entire nerve cell). The distant nerve endings connect (make junctions) with other nerve cells and the messages are transmitted across these junctions. When these endings get sick they gradually lose their ability to pass on the messages, and it is here that cholinesterase inhibitors come in (see the explanation of what these are and how they help on page 5), especially for the nerve cells first affected in Alzheimer Disease, those involved in cognition, as mentioned above.

(ii) *“Amyloid Plaques” develop all over the brain.* These plaques are dense little deposits that often appear to have replaced nerve cells; they are made largely of a protein called “beta amyloid”. However, amyloid plaques are microscopic in size (as are nerve cells themselves), so they can only be seen in the microscope, which means that they can only be studied post mortem. Beta amyloid is actually split off from a much larger protein molecule known as “APP”, the splitting being done by enzymes called “secretases”. Both APP and beta amyloid are present in normal brains, but their function is still under investigation.

The key problem in Alzheimer Disease is that abnormally high amounts of beta amyloid are produced, overwhelming the enzymes and other molecules whose job it is to clear it away (they may even be impaired themselves). When the amyloid is first split off it is dissolved, but as it reaches excessive levels it begins to deposit in the form of the insoluble plaques. Both the plaques and the excessive levels

of dissolved beta amyloid are toxic to nerve cells, but how it kills them is still not totally understood, although it probably involves the production of “free oxygen radicals”, toxic substances that are probably involved in a number of diseases. What causes the excessive production of beta amyloid in the common sporadic Alzheimer Disease is still unknown, The excess beta amyloid production in familial Alzheimer Disease happens because certain inherited genes have mutated (“mutant genes”), including the gene for APP itself, and those for the enzymes that split off beta amyloid from APP. Mutated genes cause trouble!

(iii) *Tangles of a fine thread-like protein called “tau” develop inside brain cells.* Like amyloid, tau is a normal nerve cell chemical, but in Alzheimer Disease it becomes chemically altered, causing the tangles to form, and impairing tau’s key roles in nerve cells. One of these roles is in nerve sprouting, a critically important feature of self repair in the nervous system (this is discussed later in the section on promoting brain repair). 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 their distant endings and the cell body. This transport system is essential for the cell to work and survive, and the tangles disrupt it: in a sense they choke the cells to death. As already indicated, the first casualties of disrupted transport are the distant nerve endings which contact the next cells in the circuit.

There is a controversy here. Some researchers believe that the amyloid deposits not only make the nerve cells sick, but they somehow promote the development of tangles, and it is these that actually kill the nerve cells. In any event both plaques and tangles are definitely implicated. Similar



tau tangles occur in other non-Alzheimer dementias as a consequence of certain gene mutations, but in these disorders there are no amyloid plaques! To complicate the matter further, the brains of some entirely normal aged people are found to have as many beta amyloid plaques as in Alzheimer brains – and much less frequently tangles, but no dementia! Despite these confusing facts, most researchers still regard beta amyloid as the main threat, and still direct their efforts to eliminating it (see the vaccination section on page 6).

*(iv) Inflammation of the brain develops.* Whenever and wherever the body is attacked by disease or trauma, it defends itself by mounting an immune response, also called an inflammatory response. This occurs as it should in the Alzheimer brain too. Unfortunately the disease challenge is so great that the response becomes excessive, and instead of helping it actually worsens the situation. Some of the normally protective immune substances produced by the brain's immune cells (the “microglia” which rapidly surround sick nerve cells) actually promote death of cells.

The good news is that scientists are finding drugs that can inhibit the secretases that split off the beta amyloid from APP, and clinical trials are going on right now (no results yet). As well, other agents are being researched including ones that prevent the soluble beta amyloid from depositing as plaques, and agents to reduce the inflammatory response described above. These approaches, and the vaccine studies (discussed on page 6), are among the most promising to date for long-term therapy for Alzheimer Disease.

***How do drugs like Aricept™ (donepezil), Exelon™ (rivastigmine) and Reminyl™ (galantamine) work, and why only in the early stages of the disease?***

These drugs are “cholinesterase inhibitors”, and they help preserve the ability of sick nerve endings to transmit the nerve impulses to the next nerve cell in the chain, as already mentioned above. Impulses travel along nerve fibres by an electrical mechanism, but the electricity is inadequate to cross the junctions between the fibre endings and the next cell (every nerve fibre eventually branches to make lots and lots of very fine nerve endings, each having its own junction on another cell, which itself might receive hundreds and even thousands of endings). Nature invented a new mechanism instead: each arriving impulse releases a tiny



blip of a chemical called a “neurotransmitter”, which diffuses across the junction to stimulate the next cell. For Alzheimer Disease the most important neurotransmitter is “acetylcholine”, the one used by the nerve cells in the thinking and memory-making parts of the brain. (For Parkinson’s disease the neurotransmitter affected is called dopamine). After the acetylcholine has carried the message across the junction it’s critical that it be eliminated immediately, otherwise it would hang around and keep on stimulating the downstream cell; this could be disastrous (some nerve toxins are based on this fact!). The acetylcholine is destroyed by an enzyme called cholinesterase. Now, in Alzheimer Disease the blip of acetylcholine that is released by each arriving nerve impulse gets progressively smaller and smaller as the nerve endings get sicker. Cholinesterase inhibitors prevent acetylcholine destruction by the cholinesterase, and thus what little acetylcholine is released is kept intact long enough for it to act on the next cell. And it works! But eventually the degenerating nerve endings fall away from the junctions and messages can no longer be transferred across them. To

reach this point takes usually from 2 -3 years, which is why cholinesterase inhibitors only work in the short term, but remarkably, in some instances it seems to have taken as long as 8-10 years.

The consensus remains that, though not a cure, cholinesterase inhibitors are of benefit to at least a proportion of those with diagnosed Alzheimer Disease, though there is indeed an unexplained variation among individuals as to how well they respond. And as the next section explains, a promising development is the eventual use of cholinesterase inhibitors in combination with other drugs.

### *What is Ebixa® (memantine hydrochloride) and what is its promise?*

This story has to start by talking about another neurotransmitter called “glutamate”, quite different from acetylcholine in that it’s 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 (recycled). This uptake requires that the glutamate combines first with special receiving molecules on the nerve endings called glutamate receptors (also 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 (any cells) this glutamate leaks out, and in the nervous system the levels that glutamate can reach outside sick nerve cells can be so high as to be toxic, indeed quite deadly. This is one of the

reasons nerve cells die in Alzheimer Disease – their sickness could be mild, but the glutamate leakage multiplies the threat. Memantine acts by blocking the glutamate receptors and preventing the re-uptake of the glutamate into the nerve endings. Since the glutamate threat develops somewhat late in Alzheimer Disease, memantine stands as one treatment that can be effective at moderate to advanced stages of the disease. The beauty of this approach is that the drug allows enough glutamate to get back for the sick nerve endings to use it as a transmitter, but prevents the massive uptake that would be toxic to the endings. 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. So combination therapy seems likely to become an exciting therapeutic approach in the future.

### *Where does vaccination against Alzheimer Disease stand?*

There are promising developments here. A vaccine became a real possibility firstly, when the chemists worked out the composition of beta amyloid and APP and tau protein, and secondly, when the genes for familial Alzheimer Disease were identified. Knowing these genes allowed researchers to construct animal models of Alzheimer Disease, using “genetic engineering” to get these mutated human genes into mice. The brains of these mice develop amyloid plaques just like a human Alzheimer brain, and the mice are memory-impaired. The beta amyloid in their brains was significantly reduced by injecting a modified beta amyloid that stimulates the production of antibodies against the existing beta amyloid in their brains. Following the very promising results of the first trial of this vaccine with the mouse models of Alzheimer Disease, human trials were rapidly undertaken, only to be dramatically stopped in 2002 when some of the participants developed alarming brain inflammation.

So where do we stand? Well, new antibodies are being vigorously sought that will not have the adverse effects on the brain. This must pay off eventually, and in the opinion of many will revolutionize the treatment of Alzheimer Disease. Also new mouse models are now being produced with “neurofibrillary tangles” in the brain cells, so anti-tangle antibodies will eventually be made and tested.





Much remains to be found out. But all of these pioneering studies are exciting, and give definite hope for eventual vaccination therapy.

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

*(i) MCI:* some important developments relate to “Mild Cognitive Impairment” (MCI), a condition that is being increasingly found in middle age and even young adults. In MCI there is a level of cognitive and memory impairment beyond that expected for normal aging but not bad enough to be called dementia or Alzheimer Disease. However, 10 -15 % of MCI individuals per year go on to develop the full-blown disease. Brain imaging is showing that abnormal changes may already exist in the brain before MCI is diagnosed, and indeed in some people’s brains before they develop symptoms of Alzheimer Disease. These imaging approaches, added to psychological testing, should therefore make it possible both to pick out the most at-risk MCI individuals, and to make early diagnosis of Alzheimer Disease a reality. The importance of early diagnosis lies in the fact that the best time for treatment is always as early as possible, in Alzheimer Disease as in other diseases.

*(ii) Statins:* these cholesterol-reducing agents are being investigated because the incidence of Alzheimer Disease appeared to decrease in people using these drugs for lowering their cholesterol levels. The decreased incidence of Alzheimer Disease could be because lowering the

cholesterol reduces the incidence of vascular disease, which is a risk factor for Alzheimer Disease. However, new research is showing that statins could also work in other ways that have nothing to do with reducing cholesterol levels, so here is another promising future treatment strategy.

*(iii) 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 decrease their risk of getting Alzheimer Disease, and this lead is being followed up.

*(iv) Other therapeutic remedies:* Alzhemed™ is one of a new class of drugs being tested, that either interacts with the dissolved beta amyloid before it has a chance to deposit out to form the toxic amyloid plaques, or encourages the mopping up of the beta amyloid before it reaches threatening levels. The proposal that copper, iron and other metals constitute risk factors in certain individuals is also 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, an herbal supplement purported to improve memory, is in clinical trials to see if it affects the onset or severity of Alzheimer Disease.

*(v) Stem cells:* researchers are very excited at the prospect of replacing lost nerve cells in Alzheimer brains by using “undifferentiated”, “stem cells” derived from bone marrow and other tissues; such cells, sometimes called “primitive” cells, have not yet reached the stage when they become a specific cell type like a nerve cell or a muscle cell. At this stage they can be made to change into nerve cells (or other kinds of cells) by appropriate “growth factors” (see following section); this is usually done before the cells are implanted into the brain. However, in favourable circumstances stem cells spontaneously convert to nerve cells after they’re implanted in the brain. The stem cell approach is being studied in experimental animals, and in some countries it has already been tested in people with Alzheimer Disease, with ambiguous results. It seems likely that one day human stem cell trials will become more general after ethically acceptable sources of these cells have been agreed upon and after effective and safe ways to introduce them into the brain have been worked out.



*(vi) 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 Disease are to be restored, the brain damage must eventually be reversed. Even when a truly successful treatment for Alzheimer Disease appears, i.e. one that actually stops the disease in its tracks so that there's no further brain degeneration, there's still the need to repair the damage that's already happened. We not only have to bring the disease to a halt, we have to cure the person with it! Of great importance here is a class of substances called "growth factors". These substances are nourishing molecules that the body makes continuously throughout life to look after all sorts of cells, including nerve cells, and keep them healthy. One critically important growth factor, the first such to be discovered, is called "nerve growth factor", or NGF for short. NGF is needed to keep the nerve cells involved in memory and learning alive and well (these are the ones that use acetylcholine as their neurotransmitter). Growth factors also stimulate nerve cells to sprout new endings to make up for those lost as neighbouring nerve cells die (this helps recovery after stroke and brain trauma). This "compensatory nerve sprouting" doesn't occur so readily in aging, and it is also reduced by some of the known risk factors for Alzheimer Disease. Scientists are now implanting genetically engineered cells that make NGF into the brains of animal models of Alzheimer Disease (see page 6). In some studies the cells are encapsulated within tiny containers from which the NGF diffuses into the brain. In recent studies, NGF-producing cells were implanted into the brains of people with Alzheimer Disease, and initial results show promise both for keeping nerve cells from dying and in improving cognition.

### *Social/Psychological Research*

#### *Caregiving and quality of life research*

Researchers are examining the needs of people living with Alzheimer Disease and their caregivers. They are seeking ways to improve caregiving techniques so as to enhance the quality of life for both the caregiver and the person with the disease. Here are some examples of such research, including ones that were deemed fundable by the Alzheimer Society Research Program's Social/Psychological Review Panel:

- Cognitive rehabilitation is a new area of research for people in the early stages of Alzheimer Disease. This new area of research might well relate to the “exciting proposal” discussed in the next section. Study participants are taught new strategies to help them recall important information and go about their daily tasks. These improvements, which temporarily restore independence in the person with Alzheimer Disease, are also expected to provide some respite for caregivers in the short-term.
- Completed research in 2004 has confirmed that short-term intensive counselling, in conjunction with available support, can reduce long-term risk of depression among spouses caring for people with Alzheimer Disease. Telephone-based support and information intervention helps reduce caregivers’ cortisol levels (a hormone associated with depression and stress).
- Several studies are taking place to assess the driving abilities of people with Alzheimer Disease. A US research project is studying whether deterioration of visuospatial skills could be used as an indicator to help decide when someone with Alzheimer Disease or a related dementia should stop driving. The Alzheimer Society of Canada is funding a study that focuses on solving the emotional problems faced by a person with Alzheimer Disease who has to stop driving. The Canadian Institutes of Health Research (CIHR) are funding a five-year initiative to “improve the health, safety and quality of life of Canada’s older drivers through research.”
- A national study headed by the Victoria Order of Nurses (VON) is focusing on the need for respite for family caregivers. Family caregivers need to be encouraged to take care of themselves by taking a break from their caregiving responsibilities. The study has far-reaching impact on health policy and service delivery.
- A research project that focuses on male caregivers and their special needs is studying the unique health hazards experienced by elderly men who care for their spouses. Another study is trying to find ways of helping sons who care for parents with Alzheimer Disease or a related dementia.
- Quality of life is an important outcome measure in Alzheimer Disease. A pilot study identified that people



with mild to moderate Alzheimer Disease could reliably rate their quality of life using measurable outcomes. Interestingly, their caregivers rated the person’s quality of life lower than the self-ratings of people with the disease. Further research is being conducted in this area.

- Issues such as pre-admission, overall philosophy, staff attitudes and caregiver-resident relationships are being studied to establish acceptable measures of care provided in long-term care facilities. A national web-based learning program for staff in these facilities shows how distance learning is an efficient way of upgrading skills and knowledge of Alzheimer Disease and dementia care. Another study is focusing on adult day programs and quality of life.
- Many people with Alzheimer Disease live alone in the community. Data are being gathered to predict who is at risk when living alone.
- A personalized computerized device is being tested for its effectiveness at providing verbal reminders to someone with Alzheimer Disease. This has the potential of reducing the need for caregiver assistance.



*An exciting proposal: caregiving could be promoting brain repair*

It is well accepted by researchers that nerve sprouting from surviving nerve cells is a key feature of repair in the diseased or damaged nervous system. ApoE is an important substance that plays a critical role in this sprouting. However, in humans the “apoE4” form of apoE actually inhibits sprouting. Nerve sprouting is induced by the body’s own “growth factors”, NGF being a very important one as already mentioned. However, it is now also well established that there is another important way to induce nerve sprouting; this is by initiating impulses in the nerve cells (“driving” them). Experimentally this is done by electrically stimulating them. In life it is done especially well for brain cells by increasing the “sensory input”, that is by providing 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 and generally interacting with the individual. This means that the more of this “social stimulation” a person with Alzheimer Disease gets, the more likely it is that their surviving brain cells will be induced to sprout and restore lost connections with other nerve cells. The caregiver, family member, anyone involved with the person, clearly has a critical role here. We should never be put off by absence of response (after all, nerve sprouting and the subsequent making of connections with other nerve cells takes weeks and even months). Now this proposal has obviously not been proven experimentally in humans, but a lot of animal research would support it (and this writer is especially keen on it!). The emotional benefits of maintaining contact between people with Alzheimer 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 (without overdoing it; this could cause distress to both sides!).

Additional projects presently or recently funded by the Alzheimer Society Research Program:

- Day centres and how successful they are in improving quality of life
- How to deal with the issue of using restraints
- How to assess the risks of elderly people living alone
- Do dangerous interactions occur between commonly used herbal and conventional medications?
- Should disturbed sleep in people with Alzheimer Disease be treated differently from that in normal people?
- What technology exists that could assist people with memory problems?
- Can music be a successful source of relaxation for people with Alzheimer Disease?

## *The Next Ten Years*

These are going to be exciting years. Let's look at the developments which seem most likely to pay off in that time:

Clinical trials (many have already started) will test the following:

1. Drugs that block the enzymes that split off the toxic beta amyloid from APP;
2. Drugs that clear away the accumulating beta amyloid;
3. Drugs that will help threatened nerve cells resist the disease and regenerate;
4. Drugs that will prevent the tau protein from forming tangles;
5. New vaccines that will not have the dangerous side effects of the first one;
6. New drug delivery techniques that target the regions of the brain where they are needed;
7. Updated non-invasive imaging techniques that will dramatically improve early diagnosis and show whether treatment strategies are reducing plaque density;
8. New approaches to measure chemical levels in the blood and in the Cerebral Spinal Fluid to help in early diagnosis and in evaluating if treatments are working;
9. New promise of early diagnosis based on findings from the pattern of brain waves (the EEG);
10. New cognitive training regimens that will help slow down the decline in brain functioning.

## *The Researchers*

*Biomedical researchers* try to understand exactly how adverse changes are triggered and maintained in the Alzheimer brain, and are trying to design treatments to prevent their development. As well, they are actively following a variety of approaches to promote brain repair.

*Social and psychological researchers*, including health professionals, try first to identify the personal, social and environmental factors that affect the quality of life of the person with Alzheimer Disease and of their caregivers, and then they try to improve these.

*Clinical researchers* (these are represented in both of the previously listed research areas) extend the studies of the laboratory scientists to humans, for example by carrying out trials of new drugs and other therapeutic approaches. They also participate in brain imaging that both confirms diagnosis and adds to the evaluation of treatment, and they work with other health-care professionals to improve the person's quality of life.

Finally, all the researchers involved in Alzheimer Disease help solve the ethical issues especially to do with "informed consent" and with privacy concerns in genetic testing.



### *Where does the Alzheimer Society come in?*

The Alzheimer Society is a leading funder of Alzheimer research and research training in Canada. In 2005, the Society (with our partners) funded 25 new grants and training awards, amounting to almost \$3 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. Canadian scientists rank among the top Alzheimer scientists in the world. 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)
- Heart and Stroke Foundation (HSF)
- 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)

*ASC and its partners support biomedical and social and psychological research projects in essentially all the areas discussed in this Research Report.*



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# Alzheimer *Society*

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