

**Alzheimer's disease:**  
What's it all about?  
Where do we stand in the search for a cure?



hope. courage. progress.

# Alzheimer's disease:

What's it all about?

Where do we stand in the search for a cure?

*This report describes the state of our knowledge about Alzheimer's disease as it stands today, and does so in a way that people without a lot of knowledge of science or medicine can understand.*

– DR. JACK DIAMOND, FORMER SCIENTIFIC DIRECTOR EMERITUS, ASC OCTOBER 2011

## Dr. Jack Diamond

*Dr. Jack Diamond is the former Scientific Director Emeritus of the Alzheimer Society of Canada. For the past few years, he has been giving presentations on Alzheimer's disease to various, largely lay, audiences across Canada and internationally. This report was created in the light of these presentations and takes into account questions often asked by audience members.*

*Dr. Diamond received his PhD and subsequently his medical degree at the University of London, in 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 was the founding chair of the original Department of Neurosciences when the new medical school was established at McMaster*

*University in Hamilton, Ontario, and is currently Professor Emeritus in the Department of Psychiatry and Behavioral Neurosciences, where he continues to run his laboratory research program with a special focus on the apoE4 risk factor for Alzheimer's disease. Dr. Diamond was formerly Associate Director for Scientific Affairs at the Montreal Neurological Institute at McGill University. He was a longstanding member of the grant review committees of the Juvenile Diabetes Research Foundation International, and he also served on the Scientific Committees of the ALS Society of Canada and the Spinal Cord Society. He is widely published, having written more than 75 papers in refereed journals, and 15 book chapters.*



*The future is hopeful. We have a much greater understanding of Alzheimer's disease today than we did 100 years ago, and we now know several ways to reduce the chances of getting the disease.*

**I**t has been just over 100 years since Dr. Alois Alzheimer identified the disease that now bears his name. Since that time, there have been many discoveries about the nature of the disease, its causes and risk factors, and even treatments to slow its progression. At the same time, there is much to be learned. This report describes the state of our knowledge about Alzheimer's disease as it stands today, and does so in a way that people without a lot of knowledge of science or medicine can understand.

The first section addresses some questions people commonly ask. Is Alzheimer's disease different from dementia? Why do people talk of "early" and "late" onset Alzheimer's disease? And, originally called "senile dementia," now it's Alzheimer's disease: why?

An understanding of Alzheimer's disease requires a fairly detailed look at the role of the "plaques and tangles" in the brain, and an awareness of the loss of nerve cells. This report examines how plaques are formed, the nature of tangles and why they are so dangerous, and the sickness and death of nerve cells that

cause the characteristic shrinkage of the brain.

Following this is a discussion of some of the important discoveries about Alzheimer's disease: inflammation of the brain, "oxidative stress" and the role of antioxidants, why mitochondria and glial cells are so important and why their sickness is so threatening, as is the impairment of calcium regulation. The next section includes an examination of why some people get Alzheimer's disease and others not, what the differences are between the genetic and sporadic type of the disease and the roles of both genetic risk factors and genetic protective factors. Genes and gene variants are explained, as is familial Alzheimer's disease (FAD) and its relation to animal models.

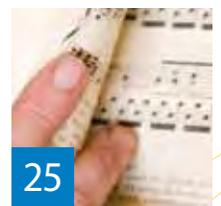
The section on the causes of Alzheimer's disease includes the amyloid or amyloid cascade hypothesis. Following that is a discussion about the risk factors for Alzheimer's disease, including aging, genetics, the ApoE4 gene variant, diabetes, and many others. There is also a discussion of how to reduce known risks for the disease, through diet, exercise, intellectual activity and so on.

Then is a discussion about diagnosing Alzheimer's disease, including the first signs typically observed, testing, how diagnosis is made, and the importance of early diagnosis. The section on treatments for Alzheimer's disease looks at drugs used to help, though not cure, the disease. Finally is a look at promising findings that could make a difference in the next five to seven years. These include, among others, vaccines; statins and secretases (drugs); anti-diabetic drugs; animal studies and the recovery of long-term memories.

The future is hopeful. We have a much greater understanding of Alzheimer's disease today than we did 100 years ago, and we now know several ways to reduce the chances of getting the disease. As well, much research is underway to help answer the many questions that remain, including the best strategies to halt and even reverse the disease process.

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*The report provides an overview of our current understanding of Alzheimer's disease. What are its origins and likely causes? Can it be prevented? What treatments are available and what are their limitations? And finally, how close are our researchers to finding a cure, making it possible not only to halt the progress of the disease, but to reverse its effects and even restore lost memories?*

## The Alzheimer Society of Canada

The Alzheimer Society is the leading nationwide health charity for people living with Alzheimer's disease and other dementias. Active in more than 150 communities across Canada, the Society:

- Offers information, support and education programs for people with dementia and their families and caregivers
- Funds research to find a cure and improve the care of people with dementia
- Promotes public education and awareness of Alzheimer's disease and other dementias to ensure that people know where to turn for help
- Influences policy and decision-making to address the needs of people with dementia and their caregivers.

## Alzheimer Society Research Program

Canadian scientists rank among the top Alzheimer scientists in the world. To support these scientists— trainees (doctoral students and post-doctoral fellows), and promising

“Young Investigators” beginning their professional careers—the Alzheimer Society of Canada (ASC) has become a leading funder of Alzheimer research and research training in Canada, distributing (with our partners) up to about \$3 million each year. The funding for the research program comes from provincial and local Alzheimer Societies across Canada, and from the generosity of individuals and corporations. The ASC administers the research program. Research applications received for the annual competition are reviewed through an extensive peer review process, and funding is provided both for biomedical and quality of life fields. ASC seeks out partnerships to enhance the impact of its research funding.

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

## Use of Information

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# common questions about alzheimer's disease

The first three sections deal with frequently asked questions about the general nature of Alzheimer's disease: how does it differ from dementia and why was senile dementia renamed Alzheimer's disease? What's meant by "early onset" and "late onset" Alzheimer's disease? How can we recognise the disease (memory loss is not always first) and why is it fatal? Finally comes the reason why Alzheimer's discovery of the "plaques and tangles" was so important – it identified the condition as a disease, not just an inevitable consequence of aging.

## Is Alzheimer's disease different from dementia?

Dementias are a large class of brain disorders characterized especially by a deterioration of thinking ability (cognition), and memory<sup>[1]</sup>. Alzheimer's disease is one such dementia, the most common one. Some dementias, called *reversible dementias*, are a secondary consequence of primary conditions such as infections, kidney disease, brain tumours, liver failure, etc. In these types of dementia, if the primary disorder can be cured, the dementia disappears. Dementias like Alzheimer's disease (often termed *Alzheimer's disease and related dementias* or *ADRD*) are not secondary to another disease but are primary disorders of the brain, and—unhappily—are often called *irreversible dementias*.

This report focuses specifically on Alzheimer's disease. Alzheimer's disease usually progresses slowly, over years, but the severity and rate of decline are extremely variable from person to person. In many instances, the disease is preceded by years of mild cognitive impairment (MCI). MCI is often regarded as a "pre-Alzheimer's" condition, in which true dementia is absent, the affected person is able to look after himself or herself, but nevertheless thinking ability is detectably reduced. What happens in Alzheimer's disease is that the nerve cells in the brain become sick and progressively less and less able to pass on messages to other nerve cells; eventually

they die. It is the loss in their connectivity—their ability to talk to one another—that is responsible for the symptoms of Alzheimer's disease, and this occurs long before the cells die<sup>[2]</sup>.

Contrary to what people often assume, an obvious memory impairment is not always the first—and most family members would say the most troubling—symptom to appear in Alzheimer's disease<sup>[3]</sup>. Nevertheless, forgetfulness does gradually increase, and in the later stages the individual may fail to recognize even close family members. Commonly, family members are the first to notice the changes. They may report a gradual decrease in the ability to carry out normal activities such as reading, driving and cooking. As well, there is a gradual emergence of problems to do with managing money, paying bills, and making judgments and appropriate responses to everyday issues. Quite frequently, the person repeats, sometimes within minutes, what he or she just said. There can be behavioural changes such as agitation, aggression, depression and even paranoia, though these tend to develop later, as do impairments of balance and movement (causing falls). Persons with Alzheimer's disease are more prone to developing epilepsy than others, apparently due to an exaggerated tendency of the brain's nerve cells to discharge messages (*impulses*)<sup>[4]</sup>, but there is no evidence that epilepsy itself is a risk factor for the disease. Not infrequently, people

with Alzheimer's disease are found wandering, unable to find their way even in familiar surroundings.

In time, affected people cannot look after themselves, and caregivers become essential for all aspects of daily living. The disease is ultimately fatal; the combination of inactivity, loss of appetite (which may result from the reduced blood flow in the Alzheimer brain<sup>[5]</sup>), muscle wasting, and a reluctance or inability to cough, together with the associated lowering of the body's immune functions, makes infections common, and in particular pneumonia, the commonest cause of death, which usually occurs within seven to 10 years after diagnosis<sup>[6]</sup>.

## Why do people talk of "early" and "late" onset Alzheimer's disease?

These two distinctions came about before it was realized that the disease had two forms: the rare, genetically driven form of Alzheimer's disease, called *familial Alzheimer's disease (FAD)*, which runs in families, and the common, sporadic Alzheimer's disease. Despite their different causes, the two forms of the disease appear to be very similar, if not identical. As with the sporadic form of Alzheimer's disease, in FAD, a minimum adult age must be reached for the disease to develop. However, this age is usually significantly younger with



FAD (the disease can strike even in the 30s), and consequently it was often called *early onset* Alzheimer's disease, in contrast to the much more common, sporadic *late onset* Alzheimer's disease. Most of us now prefer that the term *early onset*, if used at all, should refer to sporadic Alzheimer's disease that was diagnosed at a significantly earlier age than the conventional age of 65 or older, an age that justifies the *late onset* label.

## Originally called "senile dementia," now it's Alzheimer's disease: Why?

It is important to establish what is wrong with the brain of someone with Alzheimer's disease: how is the person's brain different from the normal brain? Alzheimer's disease already existed well before Dr. Alois Alzheimer's time. The condition was originally regarded as a purely age-related decline in brain functions, just as there is a progressive deterioration of the body's ability to undertake physical activities. For

that reason, it was first called *senile dementia*. This view began to change (though slowly!) following Dr. Alzheimer's now-renowned report published just over one hundred years ago<sup>[7]</sup>, which showed that senile dementia was a disease, not just an aging phenomenon. Some three to four years after his report, *senile dementia* was renamed *Alzheimer's disease* in his honour. Dr. Alzheimer used a microscope to study brain tissue taken from his female patient after she died in her early fifties with senile dementia (as he knew it, although *pre-senile dementia* was often used when the affected person was below about 65 years of age). His most important observation was of the *plaques* and *tangles*, two pathological (abnormal) microscopic changes that became universally accepted as the hallmarks of Alzheimer's disease. He also noticed that many nerve cells had disappeared from the brain. The plaques can be visualized by thinking of shaking pepper vigorously all through the brain (not just on the surface), the scattered pepper grains being so small that they are invisible to the naked eye, but visible under a microscope. They are also referred to

as *amyloid plaques*, *senile plaques* and *neuritic plaques*. The tangles Dr. Alzheimer noted are abnormal microscopic appearances *inside* many of the brain's nerve cells, as though a ball of wool had become unraveled in them, hence *tangles*. It seemed entirely reasonable that the plaques and tangles were the cause of senile dementia.

Somewhat surprisingly, it took more than half a century for Dr. Alzheimer's message to really sink in—that senile dementia is a genuine disease, a disease of aging, just as we have diseases of children, diseases of women, tropical diseases, and so on. It is not just an inevitable consequence of aging, which is why the name *senile dementia* is so inappropriate, aside from being demeaning. In Alzheimer's disease, nerve cells in the brain sicken and eventually die. The decline in memory and thinking ability in Alzheimer's disease is quite different from the consequences of the relatively minor brain cell loss that can occur naturally with aging<sup>[8]</sup>, a loss that may only marginally affect memory and cognition<sup>[9]</sup>. However, as we shall see, Alzheimer's plaques and tangles can be present in the aged brain *in the absence of dementia*<sup>[10]</sup>, and this finding, plus some others mentioned later, is stimulating a new thinking about Alzheimer's disease. A most important fact we must never forget is that the name *Alzheimer's disease* refers to what we see: a person with dementia, not a brain full of plaques and tangles!

**The next three sections** present our current understanding of the brain abnormalities described by Dr. Alzheimer just over 100 years ago. What the plaques and tangles are made of, and why are they so threatening. The first casualties of the disease, observed initially in the thinking and memory regions of the brain, are described; these are the synapses, the junctions between nerve cells, the places where the cells communicate with each other. The "synaptic impairments" appear long before the nerve cells die, and are responsible for the first symptoms of the disease. Eventually the loss of nerve cells causes the characteristic brain shrinkages.

# a new look at alzheimer's plaques, tangles, and loss of nerve cells

**TO DEVISE TREATMENTS** for Alzheimer's disease, we need to know much more not only about the plaques and tangles, and what causes these to appear, but about the other abnormalities that develop in the Alzheimer brain, which Dr. Alzheimer didn't know about, but we do.

## How plaques are formed

The plaques, we now know, are made largely of a protein called *beta amyloid*, or *A-beta* for short, which is actually split off from a much larger protein known as *APP*. Both *APP* and *A-beta* are present in normal brains, and their functions are still under active investigation. Surprisingly, in low concentrations, *A-beta* may be part of the body's defences against invading bacteria and other microbes<sup>[11]</sup>.

A major event in Alzheimer's disease (perhaps the major event) is the abnormal accumulation of *A-beta* in the brain, to a level that overwhelms the enzymes and other molecules (and also scavenger cells), whose job it is to clear away *A-beta* and even the plaques. (Enzymes are special proteins that facilitate reactions between other chemicals.) Both the production of *A-beta*, and especially the processes that clear it away, appear to be defective<sup>[12]</sup>, at least in part because the impaired blood vessels in the brain, a consequence of the disease, can't adequately pick up and remove the *A-beta*<sup>[13]</sup>. Moreover, there is evidence that these fine blood vessels proliferate and become leaky, possibly, therefore, allowing hazardous substances to get into the brain<sup>[14]</sup>.

It is now accepted that the real danger comes when the accumulating individual *A-beta* molecules begin to clump together, even just in twos and threes, to form small aggregates called *oligomers*. Their continuing aggregation eventually leads to the formation of the amyloid plaques. However, it is the oligomers, not the plaques, that are the real problem<sup>[15]</sup>; they appear to be toxic to the brain's nerve cells and, by the time enough *A-beta* molecules have stuck together to

form the plaques, the damage has already been done<sup>[16]</sup>. The *A-beta* is also responsible for the increased excitability of the brain cells that underlies the tendency to seizures in people with Alzheimer's disease. (There is no evidence, however, that epilepsy itself is a risk factor for the disease)<sup>[4]</sup>.

## What are tangles, and why are they so dangerous?

*Neurofibrillary tangles*, to give the tangles their full name, are now known to be made of a protein called tau; tau is present in normal nerve cells, but in Alzheimer's disease it becomes chemically altered (*phosphorylated*)<sup>[17]</sup>. In this altered state, tau tends to pile up as thread-like tangles, preventing its normal functions. The most critical of these normal functions is to provide a kind of railroad track system inside the nerve cells and along the nerve fibres that are spun off from the cell body. The nerve messages are carried along the surfaces of the nerve fibres that extend to make contact with other nerve cells. The tau pathways are *inside* the nerve cells and fibres and, in the latter, their main job is to convey essential nutrient and instructional chemicals, and tiny organelles (structures), up and down the fibres in both directions. Interruption in this internal transport doesn't stop the nerve messages, but it does constitute a critical threat to the health and ultimately the life of the nerve cell body, which is the factory and powerhouse for the entire nerve cell. (The nerve cell includes the cell body with its arm-like fairly short extensions (like the tentacles of an octopus), called *dendrites*, and its much longer fibre which runs to other nerve cells, called an *axon*.) In a sense, the tangles choke the cells to death.

The first casualties of the compromised internal transport system are the distant nerve endings<sup>[18]</sup>, which are especially vulnerable because they're so far away from their parent cell bodies. The junctions between these nerve endings and the nerve cells they contact are called *synapses*. As





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the nerve cells become sick, the synapses deteriorate, impairing the transmission of messages to the next cell, and that's when the first symptoms of Alzheimer's disease appear. Synapses are now a prime focus of researchers to find curative therapies<sup>[19]</sup>. Another important function of the tau protein, which suffers in Alzheimer's disease, is its role in nerve sprouting. Sprouting of new branches (usually at the ends of the axons) leads to new connections between nerve cells; not only do more connections help the nerve cells keep talking to one another as the disease progresses, but new sprouts can help compensate for connections lost. A key feature in a cure for Alzheimer's disease must be a *reversal* of the damaging effects on nerve circuitry, i.e., a reconstruction of the lost connections. A new interest is therefore developing in therapies that promote nerve sprouting, including ways to normalize the altered tau protein.

## Sickness and death of nerve cells cause characteristic brain shrinkages

As nerve cells die and disappear, that part of the brain shrinks. This process, which in Alzheimer's disease first begins in the brain regions that deal with thinking and memory, is progressive, eventually affecting most parts of the brain, which consequently shrinks as a whole. The shrinkage is initially most marked, however, in the thinking and memory regions, and this is readily distinguished by brain imaging.

*The next five sections* present features of the "Alzheimer brain" which Dr. Alzheimer didn't know about, that are actually the key abnormalities underlying the disease itself (inflammation, oxidative stress, mitochondrial impairment, glial cell sickness, calcium dysfunction, and selective brain shrinkage).

# some important discoveries since dr. alzheimer's time

## 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 poison (a toxin), it defends itself by mounting an *inflammatory response*. *Neuro-inflammation* is the inflammatory response that occurs in the Alzheimer brain<sup>[20]</sup>, and, unfortunately, the disease challenge is so great that this inflammatory immune response can become excessive; the brain's immune cells (*microglia*) become overactive and, instead of helping, they actually worsen the situation by overproducing substances that can promote the death of cells<sup>[21]</sup>, possibly also contributing to the formation of tangles. Finally, though not yet proven to result from the inflammation, it seems that the disease causes both proliferation and impairments of the brain's blood vessels<sup>[14]</sup>, changes that exacerbate the difficulties the affected brain is already facing.

## Oxidative stress and the role of antioxidants

*Oxidative stress* refers to the threatening situation created when *reactive oxygen species (ROS)*, begin to accumulate faster than the body can get rid of them. ROS are normal products of metabolism, the chemical reactions that keep the body's cells alive and well, reactions that are kept going by the food we eat and the oxygen we breathe in. However, if ROS are allowed to build up, they become damaging, poisoning the cells of the body, including those in the brain. Normally, this is prevented by special molecules made in the body called *antioxidants*. Extra help comes from our intake of natural antioxidants in food, such as vitamins C and E. Unfortunately, as the disease progresses, the production of ROS increases to levels that overwhelm the available antioxidants, which themselves are reduced by a number of factors, including stress. This includes not only everyday, or *environmental*, stress, but also the *internal stress* generated whenever a

person's health is threatened, as in Alzheimer's disease<sup>[22]</sup>. Probably most of the risk factors for Alzheimer's disease contribute to this stress. And finally, the accumulating A-beta protein itself seems to increase oxidative stress but, somewhat paradoxically, in the earlier stages, before the accumulation reaches toxic levels, the A-beta acts as an antioxidant, and could represent the body's early protective response to the disease<sup>[23]</sup>. In normal aging, oxidative

stress contributes to the deterioration of the body's tissues and cells, but because it's a major component of Alzheimer's disease, oxidative stress is becoming one of the key targets of Alzheimer's treatments. Interestingly, ROS are not all bad, and they can even be used to beneficial ends, for example by the immune system, as one way to kill invading organisms<sup>[24]</sup>.



Many scientists now believe that oxidative stress is a—perhaps the—primary event in Alzheimer’s disease, responsible for the impairment of both mitochondria and calcium regulation<sup>[31]</sup>.



## Sick mitochondria: Energy regulators of the cells

Mitochondria are tiny organelles found in all cells, and their role is critically important, to do with satisfying the cell’s energy needs. Cells use masses of energy in carrying out their normal functions, like muscle contraction or the manufacture and secretion of hormones and the special substances (transmitters) that carry the nerve messages across the junctions between nerve cells (synapses). Mitochondrial impairment in Alzheimer’s disease is a key factor contributing to the sickness of the brain’s nerve cells, and the sickness of the glial cells<sup>[25,26]</sup>.

## Sick glial cells: Caregiver cells of the brain

The brain’s glial cells, which include the microglia already mentioned, are impaired in Alzheimer’s disease<sup>[27]</sup>. There are about ten glial cells for every nerve cell in the brain, and they have a huge role, a caregiving role, in maintaining the health and connectivity of the brain cells. It seems highly likely that many, and some researchers would say most<sup>[28]</sup>, of the features of Alzheimer’s disease are primarily due to direct actions of the disease, not on the nerve cells, but on the glial cells. Sick glial cells lose their ability to maintain the normal healthy functioning of the nerve cells<sup>[22]</sup>, just as sick caregivers become less able to look after their loved ones with Alzheimer’s disease.

## Impaired regulation of calcium: A key player in brain function

Calcium is a very important substance for a host of cellular functions, and in nerve cells is especially involved in the creation of nerve messages and their transfer across the synapses to other nerve cells. The concentrations of calcium inside cells have to be rigorously regulated; too much or too little can completely disrupt the functions

of the cell. In Alzheimer’s disease, calcium regulation is disturbed and nerve cell functions are impaired, eventually affecting cognition and memory storage and just about everything the nerve cells do<sup>[29]</sup>. One player in the dysregulation of calcium in Alzheimer’s disease is a gene that has mutated (changed) over time; the abnormal genes, and in this instance the consequent impaired calcium regulation, enhance the accumulation of the threatening A-beta protein<sup>[30]</sup>.

Many scientists now believe that oxidative stress is a—perhaps the—primary event in Alzheimer’s disease, responsible for the impairment of both mitochondria and calcium regulation<sup>[31]</sup>.

*The next five sections* address important concerns of family members: my father, aunt, sister, etc, has or had Alzheimer’s disease – will I get it too? Why do some people get the disease and others not (is there such a thing as “genetic susceptibility”?). What are genetic risk and genetic protective factors? The rare “Familial Alzheimer’s disease (FAD) is discussed, and how its investigation led to the creation of animal models of Alzheimer’s disease is explained.



# why do some people get alzheimer's disease and others not?



**THIS QUESTION, AND THE QUESTION,** if my mother (father, uncle, grandmother) had the disease, will I get it too? are perfectly reasonable ones, and they draw attention to the possibility that there could be an inherited genetic susceptibility to Alzheimer's disease. (This refers to the sporadic disease; there's no argument about the genetic basis of FAD). Actually, having a direct relative with Alzheimer's disease does indeed increase one's own risk of getting it, by some three times<sup>[32]</sup>. (*Direct relative* means a parent or sibling only—other family members who have, or have had, the disease don't constitute a significant risk. And for parents, it may be that it is the mother, rather than the father, who confers the greater risk<sup>[33]</sup>.) Before becoming too pessimistic about genetic susceptibility, however, it is important to see what a threefold increase actually means. On average, at age 65, five out of every 100

people will get Alzheimer's disease, and 95 will not. If every one of those 100 people had a parent or sibling with the disease, 15 (3x5) would get it, and therefore 85 would not. The extra risk of having an affected direct relative is not so huge after all.

## Genetic influences can work both ways

It is clear that there are genetic risk factors for Alzheimer's disease, and a big effort is being put into identifying them. But, in addition to genetic *risk* factors, there are also genetic *protective* factors<sup>[34,35]</sup>. Consider a group of people all the same age, from families that have never had much Alzheimer's disease, and all living very similar lifestyles (exposed to similar environmental risk factors). It is still true that some will get the disease and others will not. Why? The brain, like all tissues

and organs of the body, is equipped with protective repair mechanisms. However, the effectiveness of these protective mechanisms varies from person to person, as do all our physical and mental characteristics, because they are determined largely by our genes. It is not only "we are what we eat," but also "we are what our genes make us." Some people get colds all the time while others never seem to get them. So, one quite likely reason (aside from differences in exposure to risk factors) why some people get Alzheimer's disease and others do not is that, in some people, our genetically endowed protective mechanisms are less effective, at least in the brain, than in those who escape the disease.

## Genes and gene variants

Genes are essentially tiny discrete segments distributed all along the long strands of the chemical known as DNA, the hereditary

material present in the nucleus (the “headquarters”) of every cell. Genes regulate all the chemistry that goes on in the cells, and thereby profoundly influence, and can even be responsible for, aspects of our behaviour, our person, our minds and our bodies. Many genes undergo *mutations* (changes) in their structure over time, and when these mutations occur in the *germ cells* (male sperm and female eggs), they are passed on to the offspring. If the mutations in these inherited genes are large enough to affect the function of the gene, the consequences can be seriously threatening to the health (and even the life) of the person. The genes that cause the rare form of Alzheimer’s disease known as FAD are in the health-affecting category.

In contrast, there are many inherited genes with relatively minor mutations, called *gene variants* (also *polymorphisms*). The genes that influence the common sporadic form of Alzheimer’s disease are of this kind. These gene variants are apparently able to carry out the normal functions of the gene, although this has not always been proven. And often a key function or process in the body is achieved only through the cooperative activity of a *group* of genes<sup>[36]</sup>. It seems likely that individually identified genetic risk factors (or protective factors) for Alzheimer’s disease don’t actually work alone but as parts of a cooperative “team” of genes, whose principal function has little or nothing to do with Alzheimer’s disease.

So it seems that, coincidental to their normal function, some gene variants make the body susceptible or *possibly resistant* to certain diseases, including Alzheimer’s disease<sup>[37]</sup>. It is a sort of bargain, and we have to live with it. Our genes are essential, but their services may come at a price. A variant is classified as a genetic risk factor for a disease if it occurs more often in people with the disease than in unaffected people. In one typical study, the variant of interest occurred in 50 per cent of those with Alzheimer’s disease, *but it was also present in 35 per cent of those without*.

Clearly, the added risk for Alzheimer’s disease conferred by such a variant is going to be very small<sup>[37A]</sup>. (There is one gene variant, the apoE4 variant of the apoE gene, which is a genuinely important risk factor for Alzheimer’s disease; this is discussed in the Risk Factor section of this report). Of course, if a number of the minor risk variants were present in the same person, the effects could presumably be additive; this would explain the direct relatives risk, since there would be a high probability of direct relatives sharing some of these genes. Finally, while identifying these genetic risk factors for Alzheimer’s disease won’t help in its diagnosis or, at the moment, its treatment, over time the accumulated knowledge of the chemistry impacted by these genes could help reveal chemical reactions that could be targets for therapeutic drugs<sup>[38]</sup>.

## Familial Alzheimer’s disease and animal models

The rare familial Alzheimer’s disease (FAD) is almost totally attributable to genes that have mutated to an extent that makes them function abnormally, and the abnormal functions are responsible for the disease<sup>[39]</sup>. The abnormal genes are passed from generation to generation<sup>[40]</sup>. We don’t know what originally caused the gene mutations, nor how far back in the history of the family they occurred<sup>[41]</sup>. We do know that gene mutations can be caused by a variety of factors, including toxic agents and ultraviolet (UV) light irradiation. For example, the exposure of one’s body to UV light when sunbathing can cause mutations in genes of skin cells, and the consequent abnormal

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chemistry in these cells is responsible for the development of skin cancer. But these mutated genes aren’t in the germ cells, so they aren’t inherited. Nowadays, when FAD is suspected, family members are asked to undergo genetic testing, and, if FAD is confirmed, they are invited to participate in Alzheimer research projects.

A truly important outcome of discovering some of the genes responsible for FAD was the opportunity, through genetic engineering, to transfer such genes to mice very early in their development. The result was adult mice with brains that possess typical abnormalities of Alzheimer’s disease: in earlier models, plaques, but more recently, plaques and tangles<sup>[42]</sup>. These mice showed evidence of impaired memory and impaired ability to “think”—the latter evidenced by their selecting unfavourable choices rather than favourable ones in a variety of situations. Prospective treatments are always first tested on these animal models of Alzheimer’s disease before they are tried out on humans.

*The next section deals with our current understanding of what causes Alzheimer’s disease, and explains the status of the popular “Amyloid hypothesis” of Alzheimer’s disease.*

# what causes alzheimer's disease?

## WE DO HAVE SOME UNDERSTANDING

about the causes of Alzheimer's. It is clear that there is no single cause for the disease. Even with FAD, aging is involved in addition to the inherited mutant genes. The common, sporadic, form of Alzheimer's disease is regarded as a *multifactorial* disorder, the result of the combined effects of a number of potentially threatening influences called risk factors. (Genetic and non-genetic risk factors are discussed below, in the risk factors section of this report.) Dr. Alzheimer's plaques and tangles can be regarded as links between the risk factors on the one hand and the ultimate sickness and death of nerve cells in the brain on the other.

## The amyloid or amyloid cascade hypothesis<sup>[43]</sup>

The most popular "explanation" of Alzheimer's disease proposes that essentially *all* the brain abnormalities seen in Alzheimer's disease develop as a consequence of one major adverse event, the accumulation in the brain of the protein *beta amyloid*, or *A-beta*. As A-beta accumulates, so the toxic oligomers accumulate. The accumulating oligomers then induce all the other abnormal changes found in the Alzheimer brain (hence the term cascade). There is no question that A-beta accumulates and that this precedes the development of the plaques and seemingly also of the tangles<sup>[44]</sup>. The toxic oligomers can also initiate—or certainly accelerate—the development of oxidative stress and neuro-inflammation, two of the important "changes Dr. Alzheimer didn't know about." Why the cascade proposal is especially appealing is that it puts a single initial event as the preferred "therapeutic target"—hit the amyloid and you cure everything! Consequently, reducing the brain's amyloid has for many years been the frontrunner in the race for a cure. It still is. However, this view is being re-examined, and some research findings definitely show

that the accumulations of the plaques and tangles can occur independently of each other rather than sequentially<sup>[45]</sup>.

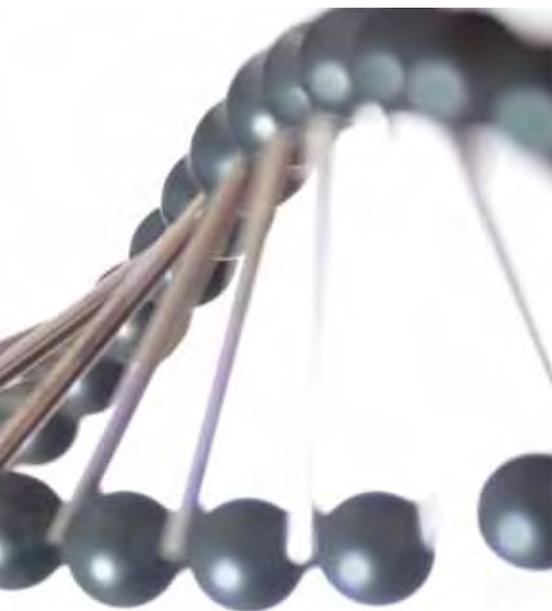
The present writer's view (and probably that of others) is this: as we get older, in some people there comes a point when the additive effects of the risk factors appear to cross a threshold, a point at which they overwhelm the intrinsic self-repair mechanisms in the brain<sup>[46]</sup>; that's when Alzheimer's disease begins. Self-repair systems are built in to all our tissues and organs, not just in the brain, and, unfortunately, their efficiency reduces as we age. (Everyone knows, for example, that broken bones or skin abrasions heal much better and more quickly in the young). Our highly protective immune systems also become less effective with age. And to make matters worse, the older the person, the longer he or she will have been exposed to the pressure of the various risk factors, some of which may actually have increased with time. Finally, the creation of new nerve cells, a feature of the normal nervous system, is defective in the Alzheimer brain<sup>[47]</sup>. So as the



defences lessen, the enemy gets stronger! While these considerations don't actually explain what causes the disease, they do help us understand it better, and help, too, in the design of strategies for combating it.

The proposed risk factors for Alzheimer's disease, almost 30, ranging from well-established ones such as aging, genetic risk factors (apoE4 being the most important), cardiovascular disease, diabetes, traumatic head injury, Down syndrome, and "Mild Cognitive Impairment" (MCI), through more recently proposed ones such as loneliness, poor diet, chronic inflammatory diseases such as rheumatoid arthritis, and depression, to more controversial ones such as smoking, prior treatment with anaesthetics, and low economic status are covered next. How some of these risk factors actually exert their adverse influence is also addressed, such as an enhancement of A-beta amyloid production and even of the neurofibrillary tangles.

# risk factors for alzheimer's disease and, when known, how they work



report notwithstanding, the concept of risk factors survives, largely because the rigorous evidence needed to establish their validity scientifically is usually difficult or even impossible to achieve with human subjects. We do the best we can, but we can't experiment with people; we can't, for example, deliberately expose people to a proposed risk factor to see if it increases their chances of getting Alzheimer's disease. What we *can* do is examine people with Alzheimer's disease and find out the extent to which they had been exposed to a putative risk factor during their lifetime. The biggest problem is that they were exposed to other risk factors at the same time, not just the one of interest. As well, the numbers of people studied in many of the reviewed reports was too few to satisfy hard-line scientists that the findings were significant.

So the evidence is not perfect; nevertheless, there is still an almost universal acceptance of the most acknowledged major risk factors for Alzheimer's disease, presented here.

Key citations for most risk factors can be found in a special issue of the *Journal of Alzheimer's disease*, (20)3, 2010. Some additional citations are provided below.

## Aging

As already indicated, aging is the most important risk factor for Alzheimer's disease<sup>[49, 50]</sup>. Whatever other risk factors are present, Alzheimer's disease never sets in until some minimum adult age is reached. This is usually well beyond 40 years, but may be significantly earlier for a person with FAD. What occurs in aging that makes it so potent a risk factor for Alzheimer's disease is being vigorously investigated worldwide. One significant finding is that at least two of the enzymes that normally function to help eliminate A-beta become less plentiful with increasing age, whether or not Alzheimer's disease is present<sup>[51]</sup>. Although aging would appear to be the one risk factor that we can do least about, this perception may

change one day. A huge amount of research is going into finding out the causes of the progressive deterioration of our tissues and organs, including the brain, that accompanies aging, and there is a genuine feeling among scientists that the answer is not beyond our reach.

One reason for this optimism comes from animal studies of caloric restriction. These studies have provided solid evidence that a rigorously controlled caloric restricted (CR) diet, particularly one that begins at weaning, dramatically slows the aging process, both physically and, apparently, mentally<sup>[52, 53]</sup>. A CR diet is not a starvation one by any means, but instituting an equivalent lifelong CR diet in humans is just not possible. Nevertheless, 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. From the perspective of Alzheimer's disease, it is not calendar (chronological) age that matters but brain age, something we can recognize but so far not control. Everyone knows that some older people seem to have remarkably young brains, while in contrast, some relatively young adults seem to be "old before their time"—a comment on their brains, not their bodies! 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 running down, as they do in aging.

## Genetics

First, a reminder of something mentioned earlier: there are both genetic *risk* factors and genetic *protective* factors. A very interesting question is, how do genetic and non-genetic (environmental and lifestyle) risk factors compare in their importance in Alzheimer's disease (i.e., nature versus nurture)? Some interesting twin studies help here. It can be assumed that identical twins are subject to the same genetic risk factors. If both

## RISK FACTORS ARE CHARACTERISTICS

of a person, the person's lifestyle, and the person's environment that contribute to the likelihood of getting one disease or another; they're not the actual cause of the disease. There are some twenty or so risk factors currently proposed for Alzheimer's disease. Many, such as high cholesterol levels or high blood pressure, are also risk factors for other disorders (in this instance, cardiovascular, i.e., heart and blood vessel disease), and these disorders are themselves risk factors for Alzheimer's disease. There are also, undoubtedly, risk factors we haven't yet discovered.

## A caveat

In 2010, a panel of experts reviewed a huge number of current reports on virtually all the accepted and proposed risk factors for Alzheimer's disease and concluded that, with the exception of aging and some genes, practically none of the risk factors was adequately supported by scientifically acceptable evidence! (Often, the experimental design was regarded as flawed<sup>[48]</sup>.) This

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such twins develop Alzheimer's disease, it seems reasonable to conclude that they were also subject to essentially the same non-genetic (lifestyle and environmental) risk factors. However, if one identical twin escapes getting the disease, presumably that twin was less exposed to the non-genetic risk factors than the other twin. Among the different twin studies that addressed the question posed above, the estimate of the genetic contribution to the disease was very variable, averaging about 59 per cent<sup>[54]</sup>. This writer, somewhat nervously, draws two conclusions from these and related studies: (i) environmental and lifestyle-related factors, *in addition to aging*, contribute most to the overall risk for getting sporadic Alzheimer's disease, and (ii) the risk attributable to purely genetic factors can be significant, but on its own is insufficient to cause the disease (except, of course, in the case of FAD). The geneticists may not agree! And, to be fair, it should be acknowledged that the effectiveness of non-genetic risk factors (listed below) could be influenced by genes, and could even depend on the co-existence of particular gene variants<sup>[55]</sup>; for example, the risk conferred by, say, repeated head trauma or diabetes could be significantly increased by the presence of one or other gene variant whose principal function in the body has little or nothing to do directly with the brain or with glucose metabolism.

In a few instances, it's been discovered how the genetic variants actually constitute a risk, small though it may be. (After all, the gene variant's major function probably has nothing to do directly with the causes of Alzheimer's disease.) One recently studied gene variant (the SORL1 gene) seems to cause an increased production in the nerve cells of the threatening A-beta protein<sup>[56]</sup>. Another recently identified gene (GAB2) has a variant that seems to promote the development of tangles<sup>[57]</sup>. Finally, four newly identified genes known as CLU, CR1, PICALM and BIN1 have been associated with an increased risk of developing Alzheimer's disease, one

proposed explanation (not yet confirmed) being that they in some way impair the elimination of the excess A-beta protein, thereby contributing to its accumulation in Alzheimer's disease<sup>[58]</sup>.

## ApoE4: The most important genetic risk factor

ApoE4 is a gene variant that represents the most compelling genetic risk factor for the common sporadic Alzheimer's disease<sup>[59]</sup>. ApoE4 is one of the three variants of the apoE gene, the others being the relatively benign apoE2 and apoE3 genes. (For some reason, it was decided not to use the name *apoE1* for one of the variants.) The apoE gene regulates the production of the apoE protein, whose principal job is to carry cholesterol (a fat that does not dissolve in water or blood) around in the blood to the various tissues that need it. Cholesterol is a critically important component of the cell membrane, the protective wall that encloses every cell in the body. Multitudes of special molecules that are the "targets" of substances such as insulin, hormones or nerve transmitters are embedded in the cell membrane. These membranes are continually undergoing repair in response to normal wear and tear, or are extending their area as the cell grows or divides to make new daughter cells, and so on. All this makes for a continual need for more cholesterol. The three variants of the apoE gene do not appear to be grossly abnormal like the genes responsible for FAD and, indeed, the apoE proteins manufactured under the direction of the different apoE variants may all carry out all the usual functions of apoE. However, it is quite possible that the apoE4 variant gene, in contrast to the apoE2 and apoE3 variants, is responsible for a form of apoE protein that has additional—in this instance undesirable—properties (these genes are said to have a *gain of function*), or perhaps it is simply less efficient in carrying out the normal apoE protein functions.

Since everyone has a double set of genes,

one from each parent, everyone has a pair of apoE genes. Up to about 20 per cent of people worldwide carry one apoE4 variant (inherited from one parent), and therefore have about three times the normal risk of developing Alzheimer's disease<sup>[55,60]</sup>, much the same as the small, direct family member risk explained earlier. However, about 2 per cent of people carry two apoE4 genes (one from each parent), and their risk increases to ten to 15 times. In a population consisting entirely of such double apoE4 gene carriers, about 50 per cent or more, not just the usual 5 per cent, are likely to get Alzheimer's disease at age 65 or older<sup>[55,60]</sup>. That said, it is important to note that people with no apoE4 genes can still get Alzheimer's disease, and people with two apoE4 genes can escape it. None of the other known gene variants, and very likely none of those yet to be discovered, confers a risk comparable to that of apoE4.

An important finding is that apoE4 is an adverse influence not only for Alzheimer's disease, but for a number of other neurological disorders<sup>[61-64]</sup>, suggesting that whatever abnormality this gene variant is responsible for, it is presumably common to all those disorders, something not yet fully appreciated. There is some evidence suggesting that apoE genes could be important in promoting nerve sprouting and connectivity among nerve cells<sup>[65]</sup>, and perhaps ongoing studies will show that the apoE4 variant is defective in regard to this important compensatory process. As well, it is known that the apoE4 variant somehow preferentially promotes the production of the A beta protein<sup>[66]</sup>, thereby constituting a significant risk regardless of any other attributes the apoE4 variant may have. Another new finding is that, while the apoE gene promotes the *degradation* of the A-beta protein, making an important contribution to the prevention of its accumulation in the Alzheimer brain, the apoE4 variant of the gene is impaired in this regard<sup>[67]</sup>. Finally, the apoE4 variant contributes to tangle formation, and it adversely affects mitochondrial functions



and certain of the synaptic (junctional) mechanisms involved in transferring messages between nerve cells<sup>[66]</sup>.

## Diabetes

It has been known for some years that type 2 (adult) diabetes is a risk factor for Alzheimer's disease<sup>[68]</sup>. In large part, it was originally assumed that this was because of the associated cardiovascular (blood, blood vessel and heart) disorders, and sometimes because of the obesity often associated with diabetes, all known risk factors for Alzheimer's disease (see below). In type 2 diabetes, glucose is not able to be utilized properly because the body's cells have become insensitive to insulin, which is needed for the glucose to get into cells, and in these people, insulin levels rise. Researchers have now found, using standard diabetes tests, that people with high fasting levels of insulin are hugely more likely to have amyloid plaques in their brains than those with low fasting insulin levels<sup>[69]</sup>. It has long been known that glucose is not utilized properly in the brains of people with Alzheimer's disease, perhaps because a lot of nerve cells have died. However, new findings are revealing a new diabetic risk condition. In at least some (perhaps all—we don't know yet) Alzheimer brains, the brain is itself in a sort of diabetic state; 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

conventional sense<sup>[70]</sup>.

In any event, it seems that, in the Alzheimer brain, either (i) the production of insulin (the brain makes its own insulin) is reduced, in this regard resembling type 1 (juvenile) diabetes, and/or (ii) the brain cells are becoming insensitive to insulin, like the rest of the body's cells in type 2 diabetes. In animal studies, it was found that A-beta can actually bring about a loss of the special molecules on the nerve cell surface that insulin has to bind to (*insulin receptors*) in order to do its job (one of those jobs may well be to help create memories!). This adverse action of A-beta occurs specifically at the synapses—the junctions—between nerve endings and the next nerve cells<sup>[71]</sup>. As well, in studies in which people with type 2 diabetes were receiving experimental anti-diabetic drugs designed to sensitize the body's cells to insulin, the treated people appeared to have a reduced incidence of Alzheimer's disease. It seems that the drugs were getting into the brain and helping the brain cells use the insulin available there. A number of anti-diabetic drugs are currently being tested on people with early Alzheimer's disease but who aren't diabetic in the conventional sense<sup>[71A]</sup>. Time will tell if this therapeutic approach is successful.

## Head injury

The explanation of why head injury (or traumatic brain injury [TBI]), especially repeated TBI like that experienced by football

players<sup>[72]</sup>, is such a threat as a risk factor for Alzheimer's disease is not yet clearly established<sup>[73]</sup>. One report says that an important consequence of TBI is a breakdown of the blood–brain barrier (BBB), a special feature of the walls of the fine blood vessels of the brain that keeps potentially harmful substances in the circulating blood from getting into the brain. Unfortunately, the same barrier can also keep out drugs that we'd like to get into the brain. TBI is known to bring about increases in the levels in the brain of enzymes called *caspases*<sup>[74]</sup>, ultimately leading to increases in yet other enzymes called *BACE*<sup>[75]</sup>, and this is bad news because *BACE* is partly responsible for the excessive formation of the threatening A-beta in the Alzheimer brain. But, as an example of just how frustrating research into Alzheimer's disease can be, other animal studies have found the opposite: a *decrease* in A-beta level following head injury<sup>[76]</sup>. Whatever the explanation, repeated head trauma is a definite risk factor for Alzheimer's disease, and one report found evidence that it increased the production of ROS as well as plaques<sup>[77]</sup>. Even a single blow to the head is claimed to cause subsequent increases in plaques and tangles<sup>[78]</sup>. Statins, which are discussed later, have been proposed as a particular way of reducing the risk posed by TBI<sup>[79]</sup>.

## Strokes and “ministrokes”

Strokes are often sudden hemorrhages

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(bleedings) or blockages of blood flow in the brain. Ministrokes are very small hemorrhages or blockages, so slight that they seem not to have caused any symptoms, but evidence that they had indeed occurred at some time is clearly visible when routine brain imaging is done at a later time<sup>[80]</sup>. The deprivation of oxygen and glucose due to strokes damages the brain, the symptoms depending on which brain regions were most directly affected. However, there are also reports of strokes somehow specifically increasing the deposition of beta-amyloid (A-beta) and the production of tangles, and also inducing the inflammatory responses described earlier, all adverse events that could increase the odds of developing Alzheimer's disease. Finally, it is now known that, like TBI (described in the preceding section), strokes can also increase the brain levels of the caspase enzymes, ultimately promoting the production of BACE and thus A-beta<sup>[81,82]</sup>.

## High cholesterol levels

High cholesterol levels in the circulating blood have long been associated with heart and blood vessel disorders, which are themselves risk factors for Alzheimer's disease<sup>[83]</sup>. New findings, however, are indicating that high levels of cholesterol can interfere with its important role in the construction of nerve cell membranes, especially discrete little regions of the membranes called *rafts*, where the various molecular receptors are embedded; when disturbances of cholesterol cause changes in the cell membranes, the distribution of these receptors becomes abnormal, a consequence especially damaging at the synapses<sup>[84]</sup>. As well, some of these molecules embedded in the raft regions of the membrane interact in a way that leads to the production of the A-beta protein, and, in a high cholesterol environment, this interaction is facilitated, the consequence being an overproduction of A-beta. (Not good news!)

## High blood pressure

The threat contributed by high blood pressure (*hypertension*) may result from the associated damage to the BBB mentioned earlier<sup>[85,86]</sup>. This leads to alterations in the levels of various substances in the brain tissue, especially certain proteins that can cause nerve cell damage and also increase the formation of A-beta. Interestingly, in older people with Alzheimer's disease, these effects of hypertension may not occur, explained partly because blood pressure tends to decrease in these people as they age and lose weight, and partly because of other age-related changes.

## Irregular heart rate

The observation that irregular heartbeat, or *atrial fibrillation*, is a risk factor for Alzheimer's disease is just that—an observation with no indications of why. Possibly, this condition is associated with a reduced blood supply to the brain, but this needs further study<sup>[87]</sup>.

## Mild cognitive impairment

Mild cognitive impairment (MCI) (mentioned earlier, in the section, "Is Alzheimer's Disease Different from Dementia?") is being increasingly diagnosed in early middle-aged and even young adults. Available evidence suggests that there is a high, though not certain, likelihood that these people will develop full-blown Alzheimer's disease within the following 10 years or more, although the exact extent of the risk varies according to the study<sup>[88]</sup>. Some interesting findings suggest that a sort of "pre-MCI" condition can exist<sup>[89]</sup>. People who claimed to have a subjective awareness of being cognitively impaired even when formal testing proved negative, later did proceed to a diagnosed MCI.

## The post-menopausal state

Twice as many women get Alzheimer's disease as men, a finding often attributed to the fact that, on average, women live longer



than men, and thus will represent a larger at-risk population than the male one. However, many of us subscribe to the view that it is the hormonal imbalance and hormonal deficiencies that develop in post-menopausal women that is the basis for their increased susceptibility to Alzheimer's disease<sup>[90]</sup>. One of the deficient hormones, estrogen, is known from animal studies to be neuroprotective, i.e., to have the ability to help protect nerve cells from the damaging effects of disease, toxic agents or trauma<sup>[91]</sup>.

## Down syndrome

All those with the genetic disorder Down syndrome who survive into their 40s or beyond will develop the abnormal brain changes essentially identical to those that characterize the brain in Alzheimer's disease<sup>[92,93]</sup>. However, and importantly, *not all of them will develop dementia*<sup>[94]</sup>.

The reason why those with Down syndrome develop the typical "Alzheimer brain" is because they have an extra copy of one particular "chromosome" in the cell nucleus. Chromosomes are essentially long strands of the hereditary material DNA, along which the genes are located. This chromosome carries the gene responsible for the manufacture of the protein called APP, from which the A-beta



protein is split off, as described earlier. More APP means more A-beta, and thus more of all the subsequent events attributed to A-beta accumulation. These discoveries in Down syndrome explained A-beta and plaque production, and became the major evidence in support of the “amyloid hypothesis” described earlier. Further studies of why some with Down syndrome do not get dementia despite their brain abnormalities could help solve the mystery of why having an “Alzheimer brain” does not necessarily mean that an Alzheimer dementia is present.

## Chronic inflammatory conditions

Chronic inflammatory conditions as risk factors make up a diverse group, but rheumatoid arthritis and asthma are probably the most studied examples<sup>[95]</sup>. Some studies have claimed that, to the contrary, rheumatoid arthritis protects against Alzheimer’s disease, but very recent studies refute this claim<sup>[96, 97]</sup>. More studies may be needed to sort out the extent to which the anti-inflammatory drugs that people with chronic inflammatory conditions take are responsible for the apparent protection against Alzheimer’s disease.

## Inadequate “exercising” of the brain

In a twin study, those doing more intellectually demanding work were less likely to develop Alzheimer’s disease than their identical twins<sup>[98]</sup>.

In general, it does seem that lifestyles characterized by intellectual activity, decision making, and learning protect against Alzheimer’s disease<sup>[111]</sup>. Possibly these activities promote the manufacture in the brain of the “growth factors” described in a later section as being enhanced by exercise.

## Episodes of clinical depression

The link between clinical depression and Alzheimer’s disease is disputed<sup>[99, 100]</sup>. Whether the conditions associated with depression are the cause or the consequence of the depression is unclear. These conditions include cerebrovascular disease (i.e., heart and blood vessel diseases known to be associated with brain disorders), poor diet, physical inactivity, lack of social engagement, and abnormal sleep patterns; it has also been noted that vitamin B12 levels are low in clinically depressed people, and that (predictably, given this finding), homocysteine levels are high<sup>[101]</sup>. High homocysteine levels are a risk factor (mentioned later).

## Chronic stress, including post-traumatic stress disorder

The risks associated with stress may relate to disturbances in stressed people in their levels of cortisol and other normal substances made by the body as parts of its defences against vascular, inflammatory, and immunological threats<sup>[102]</sup>. The abnormal levels of these substances may cause unwelcome shrinkages in the parts of the brain associated with memory and cognition, contributing to any ongoing susceptibility to dementia.

*High cholesterol levels in the circulating blood have long been associated with heart and blood vessel disorders, which are themselves risk factors for Alzheimer’s disease<sup>[83]</sup>.*

## Lack of physical exercise

The general assumption that lack of physical exercise is a genuine risk factor almost certainly derives from the good evidence (presented below) that exercise is a well-established preventative measure for Alzheimer’s disease.

## Unhealthy eating habits

Unhealthy eating habits include low vitamin D intake<sup>[103]</sup>. Other dietary deficiencies, specifically of folate, vitamins B6 and B12, cause increases in homocysteine (the true culprit is homocysteic acid [HA], which is made from homocysteine), and this leads to increased production of A-beta<sup>[104]</sup>. It has also been found that saturated dietary fat damages the lining of the blood vessels in the brain (the BBB), allowing A-beta that’s produced in the small intestine to get into the brain<sup>[105]</sup>.

## Chronic sleep deprivation

There is evidence that chronic sleep deprivation somehow leads to increased accumulation of A-beta and of plaques<sup>[106]</sup>.

## Obesity

It seems likely that the observed association between obesity and Alzheimer’s disease is due to the recognized association between obesity and type 2 diabetes, the latter then constituting the true risk, as mentioned earlier<sup>[107]</sup>.

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## Loneliness and being unmarried

There is no solid explanation for why these two states constitute a risk for Alzheimer's disease, but their association with the disease does seem clear, and the important thing is that they are remediable<sup>[108]</sup>.

## Having a spouse with dementia

People whose spouses had dementia were up to six times more likely to develop Alzheimer's disease than people whose spouses did not have dementia<sup>[109]</sup>. It seems very likely that the stress and depression levels of caregiver spouses are high enough to constitute a risk factor, being well beyond the normal levels in similarly aged people not faced with the burden of caregiving. As well, caregivers may share the lifestyle of their spouses—a lifestyle that could include some recognized risk factors for Alzheimer's disease—and so be similarly at risk.

## Low levels of formal education and low socioeconomic status

Some of us have doubts about the validity of the risk factors of low levels of formal education and low socioeconomic status because they apply especially to people who are more likely to be exposed to other more accepted risk factors such as inadequate exercising of the brain and of the body, and unhealthy eating habits. One report flatly denies that educational level affects Alzheimer's disease<sup>[110]</sup>, but another, based on a twin study, supports the influence of education<sup>[111]</sup>.

## Smoking

Smoking is not a huge risk factor for Alzheimer's disease<sup>[112]</sup>. Former smokers and those smoking less than a half pack of cigarettes per day appeared to be unharmed

with respect to the later development of Alzheimer's disease. However, the figure for smoking up to two packs a day increased to 44 per cent, and twice that for more than two packs<sup>[113]</sup>! A complication in this particular research field is the existence of good evidence that nicotine itself can oppose the development of symptoms<sup>[114]</sup>, by activating the mechanism that becomes impaired in Alzheimer's disease, as explained in the Treatments section, below.

The adverse effects of smoking likely include a reduction in the brain's blood supply<sup>[114A]</sup> and, in pregnant women, a reduced oxygenation in the brains of the unborn infants<sup>[114B]</sup>.

## Anesthesia

Despite the claim that that being put under a general anesthetic for major surgery is a genuine risk factor for Alzheimer's disease<sup>[115]</sup>, some workers claim that its adverse effect on cognition is not long-lasting<sup>[116]</sup>. Another report presented evidence that the real culprit was not the anesthetic but the hypothermia (lowering of the body's temperature) caused by the anesthetic, which then enhanced the enzymatic activity in the brain cells that caused the normal tau protein in them to change into the form that created the tangles characteristic of Alzheimer's disease<sup>[117]</sup>.

## Other risk factors

There are also risk factors that are not so firmly established, such as excessive drinking and drug abuse<sup>[118]</sup>. Researchers are still examining whether some people are at risk because their bodies have difficulty handling foods containing the metals copper, iron and aluminum, although most researchers no longer regard aluminum as a risk factor for Alzheimer's disease<sup>[119,120]</sup>.

One important research thrust is finding out to what extent risk factors can exert their threatening influence by *directly* promoting one or other of the brain abnormalities associated with Alzheimer's disease. It is

acknowledged, and in keeping with the "amyloid cascade" hypothesis, that most or all of the risk factors do cause an increase in A-beta, and that this increase can initiate the development of these brain abnormalities. However, there is evidence indicating that these same abnormalities can develop *independently* of increased A-beta<sup>[121]</sup>. In the end, there is some comfort in knowing that exposure to the known risk factors does not mean that a person will definitely get Alzheimer's disease. The comfort is less, however, when we remember that one may have limited exposure to the same risk factors and yet still develop the disease. We still have a way to go before we get to the bottom of this health hazard.

The large number of such measures included here range from the most obvious, which is to avoid the risk factors just discussed and to properly manage threatening medical conditions such as hypertension, through a succession of items which collectively constitute a "healthy life style" (a good diet, physical and mental exercising, protection of the head, etc), to less well known measures such as active socialisation and (a controversial issue) hormone replacement therapy.

# how can we reduce the risk of developing alzheimer's disease?



*The brain's intrinsic protective and self-healing mechanisms are very important factors in our being able to withstand the additive effects of the risk factors we're all exposed to, and that at least some of these preventative measures work by enhancing these mechanisms.*

**AN EXTENSIVE SURVEY** of where we stand with regard to (i) identifying risk factors for Alzheimer's disease, and (ii) best approaches to preventing them and improving one's chances of not developing the disease, is provided in a special issue of the *Journal of Alzheimer's disease* 20(3), June 2010. The sections in this report on risk factors and reducing the risk provide core summaries of both areas.

Direct and compelling evidence for preventative measures is not always available, and we refer again to the 2010 report mentioned earlier in relation to risk. As for those factors, the reviewers poured cold water on the evidence for preventative measures, and largely for the same reasons (inadequate numbers of people examined and poor experimental design). Nevertheless,

a multitude of papers report that healthy lifestyles can really help reduce the risk of Alzheimer's disease, and/or to slow the disease progress once it has begun. The following list, which amounts to adopting a healthy lifestyle, identifies the various preventative measures reported to help achieve this end. This strategy not only reduces the Alzheimer risk directly, but also indirectly by reducing specific risk factors such as stress and obesity. Recent discoveries suggest that, overall, this same strategy may help in the creation of new connections between the brain's nerve cells, and, indeed, in the generation of new nerve cells. A view vigorously promoted by this writer is that the brain's intrinsic protective and self-healing mechanisms are very important factors in our being able to withstand the additive effects of the risk factors we're all exposed to, and that at least some of the preventative measures listed below work by enhancing these mechanisms.

## Avoiding known risk factors

First and foremost, people must be aware of the lifestyle and environmental risk factors listed in the preceding section, and, as far as is possible, avoid them.

## Management of relevant medical disorders

People must find out if any medical condition they have is regarded as a risk factor for Alzheimer's disease; if it is, they must give a high priority to its treatment and/or management.

## Healthy eating

The focus on healthy eating is on a Mediterranean-type diet, and especially on eating antioxidant-rich foods such as blueberries and raspberries and dark green leafy vegetables such as spinach and collard greens, which significantly reduced the risk for Alzheimer's disease, especially when coincident physical activity was

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encouraged<sup>[122]</sup>. In a twins study, the twins with a higher fruit and vegetable consumption had a reduced risk of dementia compared to their counterparts whose diet was less in this regard<sup>[122A]</sup>.

Antioxidants such as vitamin C oppose oxidative stress, which has already been mentioned as an important consequence of the actions of risk factors. Vitamin C, interestingly, has been shown experimentally also to dissolve amyloid plaques<sup>[123]</sup>. Green tea is reported to be preventative by virtue of its content of an antioxidant known as EGCG<sup>[124]</sup>, and coffee because of its caffeine content. (These studies were entirely animal ones<sup>[125]</sup>.) Also recommended by some are the antioxidants selenium and folic acid. Folic acid, also called *folate*, 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, folic acid 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. The benefits of B12 supplementation are being increasingly reported<sup>[126,127]</sup>, but are still not established to everyone's satisfaction.

A number of studies support vitamin E supplementation as a significant way of slowing down the progression of Alzheimer's disease<sup>[128]</sup>. However, caution is advised here; specifically, the intake of vitamin E should not exceed that recommended for the commercial product being used.

In related studies, apple juice supplementation was found to oppose increased A-beta levels; these increases were not due to Alzheimer's disease, but to an experimentally-created dietary deficiency of folate and vitamin E in normal adult mice<sup>[129]</sup>. Both human and animal studies support apple juice as having an inhibitory effect on A-beta production<sup>[130]</sup>. Recently, a beneficial effect of fruit and vegetable juices

was reported that appeared to be due to the presence in the juices of antioxidants called *polyphenols*, rather than the antioxidant vitamins E or C (different antioxidants target different members of the ROS described earlier)<sup>[131]</sup>. Studies in mouse Alzheimer models show convincing evidence of the protective value of grape skin-derived polyphenols against the development of Alzheimer's disease, supporting the claim that red wine is beneficial in this regard<sup>[132]</sup>. A moderate intake of alcohol generally may help prevent dementia<sup>[133]</sup>, but this report has generated a host of opposing opinions at research meetings.

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<sup>[134]</sup>. 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 mentioned earlier. However, there are reports that dampen enthusiasm for curcumin and especially for another much touted plant supplement, Ginkgo<sup>[135]</sup>. A more debatable issue relates to omega-3 fatty acids, found especially in cold water fish, flax and walnuts. The drive to increase intake of omega-3 fatty acids, especially the one known as DHA, came after findings that these fatty acids were low in people with Alzheimer's disease, and that in some studies their dietary supplementation improved cognitive functioning<sup>[136]</sup>. Now the usefulness of DHA supplementation is being questioned, following negative results in other clinical trials<sup>[137]</sup>. The definitive answer on DHA has yet to appear.

## Exercising

Exercise is well reported as beneficial where Alzheimer's disease is concerned<sup>[138,139]</sup>. 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<sup>[140]</sup>, and, in another, even modest weightlifting was effective in staving off cognitive decline<sup>[141]</sup>. There are some extremely relevant findings from animal studies<sup>[142]</sup>; exercise was shown to enhance the production in the brain of brain-derived neurotrophic factor (BDNF), an important member of the family of substances known as *growth factors*, or *trophic factors*. These factors are natural nourishing molecules made in the embryo especially to help establish the development of stem cells (immature and often recently born cells) along the road to becoming specific, mature cells with a characteristic identity, such as heart cells or liver cells. However, trophic factors are also made continuously throughout life to help maintain the health of virtually all the body's cells. When it comes to nerve cells, growth factors in particular promote their ability to maintain connections with each other and also to make new connections.

It is well accepted that the earliest symptoms in Alzheimer's disease are due to the loss of connectivity between the brain's nerve cells, the first victim of the cells' sickness<sup>[142A]</sup>. It should be mentioned here that the first discovered growth factor of significance in the nervous system was called *nerve growth factor*, or NGF, a finding that generated an entirely new field of research (and a Nobel prize for the discoverer, Professor Rita Levi-Montalcini, who has just celebrated her 100th birthday in her Italian home).

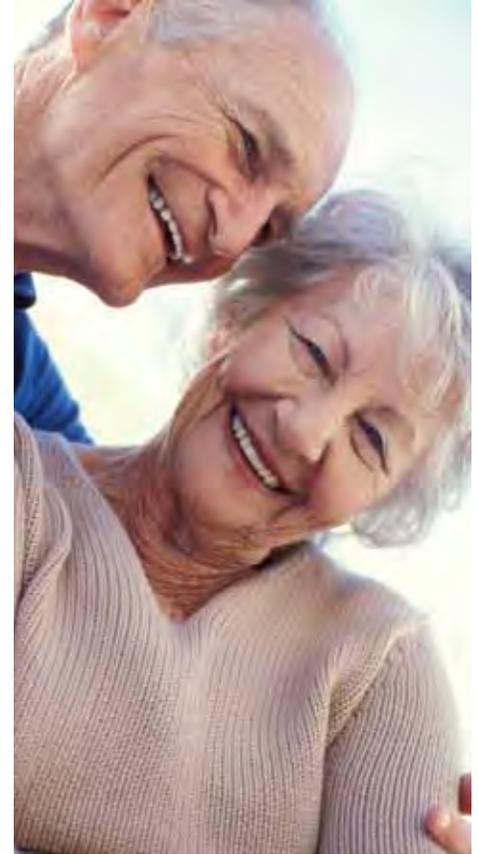
Among the many roles of NGF is that of maintaining the health and the connectivity of the brain cells especially involved in cognition and memory, cells that are the earliest victims of Alzheimer's disease. NGF is now a hot candidate for a therapy aimed at reversing the effects of the disease, even restoring lost memories. But so is BDNF, which, in the animal studies mentioned above, appeared to be involved in the increased

connectivity in the brain, an increased production of new cells (stem cells) destined to become nerve cells (precursor cells), and in a rescue of memory deficits<sup>[142]</sup>. Interestingly, a Korean group reported that BDNF levels in the blood were reduced in people with MCI and Alzheimer's disease, suggesting that this reduction could be a factor in developing the disease<sup>[143]</sup>.

One report noted that exercise in older adults improved functional connectivity among the nerve cells in parts of the brain involved in cognitive function<sup>[144]</sup>. Exercising also helps maintain a good blood supply, and therefore oxygen supply, to the brain. This is particularly important because of the evidence that when the brain is subject to hypoxia (reduced oxygen supply), A-beta production increases<sup>[145]</sup>. An interesting recent report studied the levels in the brain of a certain protein called *PGC-1alpha*, which is involved in regulating type 2 (adult) diabetes; it was found that in people with Alzheimer's disease, the levels of this protein were reduced, but were increased by exercise, an activity that also helps prevent type 2 diabetes<sup>[146]</sup>. These findings might give clues as to the links between Alzheimer's disease and diabetes, a topic addressed earlier. Finally, a twin study<sup>[147]</sup> in which comparisons are made between genetically identical (or close to identical) twins found that in those twins who had indulged in mid-life exercising, the odds of developing Alzheimer's disease *some three decades later* were significantly reduced compared to their non-exercising counterparts.

## Having a socially interactive lifestyle

Having a socially interactive lifestyle was identified, especially in the context of organized social leisure activities<sup>[148]</sup>, and included studies of twins who developed or didn't develop Alzheimer's disease<sup>[111]</sup>. For example, contributing to group discussions or group theatre-going slowed down the



progression of Alzheimer's disease<sup>[149]</sup>. Conversely, already mentioned in the risk factor section, loneliness in seniors has been linked to a higher risk for dementia, and, clearly, increased socialization would help here, including activities like spending time with family. Of note is an earlier twin study<sup>[150]</sup> that found intellectual-cultural activities to benefit women but not men in reducing the risk for Alzheimer's disease.

## Intellectual activity

Intellectual activity includes doing crossword puzzles, reading or playing chess. In one twin study, twins with a high complexity of work were less likely to develop Alzheimer's disease than twins doing less complicated work<sup>[98]</sup>. In general, it is accepted that both social interaction (discussed earlier) and the intellectual activities referred to here provide cognitive stimulation, which has become an important feature of both basic and therapeutic research. There is now good evidence that bilingualism is protective against the development of Alzheimer's disease<sup>[150A]</sup>. One problematical finding is that, although cognitive stimulation may well delay the onset of Alzheimer's disease, after the disease begins, its progress appears to be accelerated<sup>[151]</sup>.

# how can we reduce the risk of developing alzheimer's disease?

## Having close caregiving relationships

The association between close, mutual, caregiving relationships and a reduction in the risk of developing Alzheimer's disease was clear, and it could be that the reduced stress levels are implicated here in the beneficial effects of good caregiving situations<sup>[152]</sup>.

## Protecting your head

Wearing safety helmets during recreational and sporting activities obviously reduces the chances of traumatic head injury.

## Hormone replacement therapy

Despite a well publicized, large-scale clinical study on women that recommended discontinuation of hormone replacement therapy (HRT) because it appeared both to be ineffective and to have potentially dangerous side effects<sup>[153]</sup>, a number of clinical researchers continue to regard it as worthy of further study<sup>[154]</sup>. This is especially so because of studies showing that estrogen treatment of post-menopausal women effectively reduced their incidence of Alzheimer-like symptoms<sup>[155]</sup>. Moreover, animal studies are

*Estrogen treatment of post-menopausal women effectively reduced their incidence of Alzheimer-like symptoms<sup>[155]</sup>.*

pointing to the possibility that testosterone treatment could benefit men in this regard. Time will tell.

## Benefiting from music therapy

A number of reports—some anecdotal—speak to the effectiveness of music therapy, particularly when the patient is exhibiting aggressive behaviour<sup>[156]</sup>.

The accepted view today is that of the ancient Greeks, "mens sana in corpore sano"; the lifestyle that promotes a healthy body also promotes a healthy brain. This really defines 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 who have it. Adopting a lifestyle that ignores risk factors does not mean one will develop the disease, but it does increase the odds.



**Now addressed** are diagnostic approaches which range from the initial psychological and physical examination in the doctor's office to specialised procedures that include brain imaging and examination of the fluid obtained by lumbar puncture (the "CSF"). Discussed too are "biomarkers" of Alzheimer's disease. These are still at an experimental stage, and they include an examination of blood for the presence of certain proteins. Finally comes the issue of making an early diagnosis, even before symptoms are experienced.



# how is alzheimer's disease diagnosed?

the presence in the brain of the hallmarks of the disease, the plaques and tangles already described. However, this view is being questioned more and more<sup>[157]</sup>. First, abnormally high numbers of amyloid plaques and tangles were observed in the brains of very old people who died with essentially *normal* cognitive functions and memory, although we cannot be absolutely certain that they were not in a pre-clinical—i.e., pre-symptomatic—stage of Alzheimer's disease. Second, although people with Down syndrome who have survived well into their 50s and beyond all have typical Alzheimer brains, a significant number of them do not have dementia. Third, the brains of a number of relatively young people diagnosed as having MCI (a pre-Alzheimer's state) can have substantial numbers of plaques and tangles<sup>[158]</sup> but they do not have Alzheimer's disease, as evidenced by dementia. And finally, we have the results from studies of people with early Alzheimer's disease who had been receiving a vaccine against A-beta for about two years, i.e., up to the time when this treatment was stopped worldwide because of indications that it was inducing a potentially lethal brain inflammation. (Vaccines are discussed in a later section.) After some of these people died, their brains were examined; as in the earlier animal vaccine studies, the vaccine appeared to have worked: the plaques had almost disappeared. But despite this, their dementia prior to death was unchanged.

So where do we stand? If you have Alzheimer's disease, your brain will certainly be loaded with plaques and tangles. However, the presence of these hallmarks only confirms the diagnosis of Alzheimer's disease if a dementia had been unambiguously diagnosed prior to death.

## The doctor's diagnosis

In practice, the diagnosis of Alzheimer's disease is often made in the doctor's office. The doctor bases the diagnosis on the history,

present and past, given by family members as well as the person under investigation, and includes the person's general health, and especially the ability to function normally, taking account of mood, the ability to converse, personality, attention span, and a wide spectrum of activities of daily life; the results of a routine examination of the general health of the person (blood pressure, heart rate, neurological testing of reflexes, muscle strength, speech, sensation, etc.); and on the results of some straightforward psychological and memory tests. Overall, the accuracy of a "doctor's office diagnosis" is over 90 per cent<sup>[159]</sup>.

## Differential diagnosis

Which of the possible diagnoses is the correct one? The doctor may have concerns about the cause of the observed dementia, and may request additional testing at specialized clinics or hospital departments. As mentioned at the beginning of this report, a person suspected of having Alzheimer's disease could in fact have any of a number of medical conditions that are not Alzheimer's disease, but are—perhaps transiently—giving rise to genuine symptoms of dementia. These reversible dementias develop secondary to other conditions, which include psychiatric disorders such as depression and schizophrenia, or physical ones like brain tumours or abscesses, diabetes, stroke, anemia, thyroid or liver or kidney disease, infections, vitamin deficiencies or excess of alcohol. An increasingly recognized cause of dementia in the elderly is the prescription (maybe over-prescription) of medications, and/or an excessive use of over-the-counter dietary supplements. In contrast are the irreversible dementias mentioned earlier<sup>[160]</sup>. Not uncommonly, there may be a mixed dementia, for example both Alzheimer's disease and vascular dementia.

## Psychological testing

The tests used for cognitive (thinking) ability and memory usually include the

## First signs

The advent of Alzheimer's disease is signaled by the increasing occurrence of the distressing behaviours described earlier. To help alert family members, we recommend that they read our document "10 Warning Signs." The appearance of just one or two of these signs is enough to justify a visit to the doctor.

## Where do we stand on the importance of a post-mortem examination?

There is widespread belief that a true diagnosis of Alzheimer's disease can only be made after a pathologist has confirmed

# how is alzheimer's disease diagnosed?

Mini-Mental State Examination (MMSE), a series of questions that test a range of everyday mental abilities and knowledge, an understanding of the time and date, and an ability to name objects correctly and explain similarities and differences between them<sup>[161]</sup>. Another popular test, the Mini-Cog, is especially effective in uncovering these impairments in their earliest stages; one of its memory tests is to repeat a succession of words, and one "thinking test" is the clock drawing test (positioning the clock hands on a sketched clock face to show times selected by the examiner). One reason some doctors like the Mini-Cog is because the results are not influenced by education level or language abilities. Finally, increasingly popular is a test devised in Canada, the Montreal Cognitive Assessment (MoCA), which is similar to and appears to have all the advantages of the Mini-Cog test and more, and is about as accurate as the MMSE, while much quicker and easier to administer.

## Biomarkers

Biomarkers are unusual changes that occur in association with the appearance of conventional behavioural indicators of Alzheimer's dementia. These can be measured non-invasively (i.e., in easily examined tissues like the skin, blood and urine) and, in a somewhat invasive technique, in the cerebrospinal fluid (CSF), the fluid that bathes the brain and spinal cord. Researchers are actively seeking such biomarkers, simple and unambiguous laboratory tests, especially ones that develop very early in the disease, and, ideally, well before the appearance of dementia<sup>[162-164]</sup>.

**Blood.** The most favoured tissue to examine for biomarkers is the blood. Several studies have been published suggesting that such blood biomarkers may indicate risk for developing dementia prior to its onset, or signal which individuals with MCI might be prone to progress further into full-blown Alzheimer's disease<sup>[165,166]</sup>. Other biochemical

changes have been reported in the blood of already affected people<sup>[168,169]</sup>. However, these studies have been focused on relatively small groups of patients, and have been difficult to replicate despite multiple attempts to do so. While the benefits and importance of pursuing such studies is obvious, and despite the aggressive efforts by many research groups, it remains speculative at this point whether the brain disorder associated with Alzheimer's disease will indeed have a signal in blood that will be useful in diagnosing the disease or signaling its progression.

However, it is intriguing that a progressive reduction in hearing<sup>[171]</sup> and in smell<sup>[172]</sup> have been reported to occur well before a diagnosis of Alzheimer's disease is made, and the steady weight loss normally associated with aging was reported to double in the year immediately preceding the appearance of Alzheimer-like symptoms, although another report claims that pre-symptomatic weight loss occurs only in women<sup>[170]</sup>. Thus, while still speculative, the possibility remains that there may be biomarkers outside of the brain, justifying the continued search for them<sup>[167]</sup>.

**Lumbar puncture.** A far more validated and established indication of risk for Alzheimer's disease relies on examination to reveal characteristic abnormalities in the levels of certain proteins (A-beta and tau-related ones especially) in the CSF<sup>[163,173]</sup>. CSF is obtained by lumbar puncture (spinal tap). This procedure is not without risk, and certainly is less acceptable than routine blood draws in medical examinations. Nevertheless, it is commonly done in many European countries, and growing in acceptance throughout most of the world. The diagnostic accuracy of the protein changes in the CSF make it a worthwhile and acceptable procedure for the potential diagnosis of the disease<sup>[174]</sup>.

**Brain imaging.** Among the additional tests a doctor may request are a variety of *imaging procedures*, especially to assist in a difficult diagnosis<sup>[9]</sup>. Magnetic resonance imaging (MRI) and computed tomography (CT)

scans give valuable information about the shape and volume of the brain. The brains of people with disorders such as Alzheimer's disease shrink significantly as the disease progresses (largely due to the loss of nerve cells), and the regions of the brain most and earliest affected vary from disease to disease, thereby helping in the diagnosis<sup>[175]</sup>. Positron emission tomography (PET) and functional MRI (fMRI) reveal how well the brain's nerve cells are actively using the sugar and oxygen brought by the brain's blood supply (oxygen and glucose use significantly reduces in the diseased brain), and which brain regions are most affected. An imaging approach called *Magnetic Resonance Spectroscopy (MRS)* is able to reveal the presence and levels of a variety of biochemical substances called metabolites, and there is a possibility that the ratios of some of these metabolites might alter in a characteristic way when one's cognitive function is impaired<sup>[176]</sup>. And finally, new imaging techniques are emerging (they're not yet widely available outside of research facilities) that make it possible to study the plaques and more recently the tangles during life rather than post mortem.

These techniques use special radioactive chemicals that are injected into the blood circulation and thereby reach the brain. There, the chemicals (sometimes called *tracers*) attach to the A-beta, which forms the plaques, and there's now a new tracer that attaches to tau, the protein associated with the tangles<sup>[177]</sup>. The tracers become concentrated as they attach to the plaques or tangles to the extent that they are easily visualized in the imaging procedure, allowing the numbers of plaques and the tangles to be evaluated without the need for surgery and exposure of the brain to provide biopsy material for microscopic examination. Two special attractions of these new imaging approaches are, first, that they may help in distinguishing Alzheimer's disease from other dementias and, second, that repeated imaging sessions should also show whether treatments are working, since these would be expected to reduce

or eliminate the initial abnormal features revealed by the first imaging.

## Genetic testing

The confidence that a correct diagnosis has been made may be strengthened by confirming the presence of genes that constitute risk factors for Alzheimer's disease, but from a practical perspective, this comment applies to only one gene: the apoE4 gene (see earlier discussion of genes)<sup>[178, 179]</sup>.

## Early diagnosis: New proposals

As we've already seen, new studies are finding evidence of plaques and tangles in the brains of people who have been diagnosed not with dementia but with MCI<sup>[180]</sup>, and in the brains of very old people with no evidence of either MCI or Alzheimer's disease<sup>[181]</sup>, so an accurate early diagnosis of the disease is truly problematic. Some four years ago, a Canadian-led study proposed new criteria for the diagnosis of probable Alzheimer's disease<sup>[182]</sup>. These included a progressive memory loss over more than six months plus at least one or more of the following biomarkers: MRI-revealed atrophy (i.e., shrinkage; see earlier imaging section) in the temporal lobe of the brain, abnormal protein levels in the CSF, reduced glucose utilization in the brain shown by PET scanning, and the presence of at least one genetic risk factor for Alzheimer's disease in the immediate family.

More recently, a series of recommendations for diagnosis was produced by a group of experts organized by the National Institute on Aging, which is part of the U.S. National Institutes of Health (NIH), which governs medical research in the United States. These tests are the subject of a very useful commentary in the 2011 *Journal of Alzheimer's and dementia*<sup>[183]</sup>. The recommended tests are similar to the ones described earlier, specifically, routine brain imaging to reveal shrinkages, examination



of CSF protein levels, genetic testing, and now adding psychological testing. However, it was suggested that, at present, the battery of proposed tests should be restricted to research facilities, and that it be undertaken not only to confirm the diagnosis of Alzheimer's disease in its early stages, but to pick out the most at-risk MCI individuals (the ones most likely to progress toward the full-blown disease), and to detect even entirely pre-symptomatic people. The last is obviously a tough call. Why would perfectly normal people want to find out if they were especially at risk for developing Alzheimer's disease? Presumably, tests on asymptomatic people would be restricted to persons who, for family history or other reasons, believe themselves to be at a higher risk than normal for getting the disease. There's no question that in any

disease the sooner a therapy is started the better, and we *will* have such therapies within a few years; hence the importance of early diagnosis.

A Canadian group has discussed the implications of the NIH proposals for Canada, and has recommended similarly that these new diagnostic criteria, admirable though they may be, are currently unsuitable for use in general clinical practice<sup>[184]</sup>. Incidentally, a recent report claimed that, using MRI alone, it was possible to detect an atrophy (brain shrinkage) characteristic of Alzheimer's disease almost ten years before a dementia was actually diagnosed<sup>[185, 186]</sup>.

Readers especially interested in diagnosis may care to look at our own (ASC) Information Sheet.

Now we turn to the treatments currently available (e.g. Aricept and Ebixa (Memantine)), drugs which are essentially symptomatic, i.e. they don't oppose (modify) the actual disease process), their strengths and their weaknesses such as adverse side effects, and – when they're effective at all! – limited duration of effectiveness and anticipated "disease-modifying" drugs currently in clinical trials.

# treatments for alzheimer's disease

## THE DRUGS DISCUSSED IN THIS SECTION

to treat Alzheimer's disease help but they don't cure, i.e., they're *not disease modifying*<sup>[187]</sup>. Rather, they delay, or at least significantly slow down, the symptoms for periods that commonly can last for 1–3 years. Unfortunately they don't work on everybody (it's not clear why), although some patients claim that the benefits have lasted for much longer – even up to 7 years! Moreover others ask for these symptomatic treatments to be discontinued because of the miserable side-effects, especially the gastro-intestinal ones. The problem is that the “targets” of virtually any drug (the special molecules the drugs will interact with, called “receptors,” are the targets) are rarely confined to a single organ or tissue, the brain, say, but occur elsewhere in the body (an example of nature's economical approach – if a mechanism works well in one place, then it's used in other places, too.). And there's the rub! A drug designed to act on certain cells in the brain, for example, usually can reach and act on any regions of the body that are using the same receptors, and that's why we have “side effects.”

However, this author has so often seen faces among his audience light up when they at last understand why these Alzheimer drugs don't really cure—and why they are effective for so few years—that the decision was made to explain just how these particular drugs work—and stop working. It is hoped that what follows does not give the reader a false sense of the importance of these drugs. But they're all we've got right now, so let's at least understand their critical limitations.

## Cholinesterase inhibitors: Aricept™ (donepezil), Exelon™ (rivastigmine) and Reminyl™ (galantamine)

Cholinesterase inhibitors 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



consistently effective cholinesterase inhibitors didn't appear until 10 years later, when along came the new generation of these drugs, which are still in use. How they work makes a fascinating story.

Nerve messages, or impulses, travel along the surfaces of nerve fibres by an electrical mechanism, but the electricity is inadequate to cross the junctions (synapses) between the nerve and the next cell, which means that, without help, the nerve message would end there. 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, or excite, a new impulse in the next cell. For Alzheimer's disease, the most important neurotransmitter is acetylcholine, the one used especially by the nerve cells in the thinking and memory-making parts of the brain. Now the brain uses a number of different neurotransmitters, and certainly their dysfunction contributes to what we see in Alzheimer's disease. But an acetylcholine impairment was the first to be identified in this context, and most of us believe that its reduced production as the disease progresses contributes more than any

other neurotransmitter dysfunction to the disease symptoms, certainly the early ones.

Back to acetylcholine, after the nerve message has arrived and the released blip of acetylcholine has crossed the junction, it reaches and reacts with the receptors attached to the receiving cell and that reaction starts off the message in the receiving cell. It is critically important that the acetylcholine be eliminated immediately; otherwise it would keep on stimulating the downstream cell (imagine a message being repeatedly shouted again and again and again into your ear!). 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 has delivered the message, and this is achieved by an enzyme called *cholinesterase*.

In Alzheimer's disease, the blip of acetylcholine released by each arriving nerve impulse gets progressively smaller and smaller as the nerve cell get sicker and sicker, eventually becoming too small to transmit the message across the junction. (This is when the symptoms of the disease first appear.) Cholinesterase inhibitors prevent cholinesterase from destroying acetylcholine, and thus what little acetylcholine is released per impulse eventually build up to levels high enough to get the message across to the next cell and it can work. However, in time, the sick nerve endings degenerate to the point where no transmitter is released at all, and the drugs are then totally ineffective. The best news is that it seems to take up to two or three (or even more) years to reach this point, since cholinesterase inhibitors can often be effective for a few years, even one year. This means that when we find, as we will, treatments that can “rescue” sick nerve cells, there is a huge window of time for such rescue to be achieved.

This finding fits in with evidence that another apparently quite unrelated action of cholinesterase inhibitors is somehow to protect nerve cells from damage by oxidative

stress<sup>[188]</sup>. It has to be acknowledged, though, that there is a significant 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, drug companies have developed a new method that gets the drug into the body without going by way of the gut, which is the source of many of the undesirable side effects. Cholinesterase inhibitors are not swallowed but are contained in a patch, which is attached to the skin, allowing the drugs to be absorbed directly into the body. The usual problem of patch administration is in 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, and despite their off-putting side effects, cholinesterase inhibitors are of benefit to at least a 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®. A caution, however: overuse or too high a dosage of cholinesterase inhibitors could increase

the possibility of seizures, because the enhancement of message transmission across the synapses could lead to overstimulation of the downstream nerve cells; this effect would almost certainly occur if normal people were to receive this treatment, a fact that was taken advantage of in the creation of some of the First World War poison gases! Finally, the receptor molecules acted on by the acetylcholine also accept nicotine molecules, and this is why nicotine administration can to a degree make up for the progressive reduction in acetylcholine as the disease progresses. (This was referred to earlier, when smoking was discussed.)

## Ebixa® (memantine hydrochloride)

This story has to start by discussing another neurotransmitter, glutamate. Unlike acetylcholine, glutamate is not destroyed by an enzyme after conveying the message across the junctions between nerve cells. Instead it is taken back up into the nerve endings from which it was released, or in other words, it is recycled. This uptake requires that the glutamate combine first with special receiving molecules on the nerve endings, called *glutamate receptors* (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.

The drug 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 seems to get 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. As we learn more and more about the different processes affected in Alzheimer's disease, combination therapy, with different drugs attacking different targets, seems likely to become an exciting therapeutic approach in the future.

## Disease-modifying drugs

A number of drugs designed to reduce the splitting-off of A-beta from APP, help eliminate the excess A-beta, or prevent the sticking together of its molecules to form the toxic oligomers, have undergone clinical trials over the past ten years or so, and they have all failed, despite the apparent success they had on mouse models of Alzheimer's disease. The therapeutic possibilities of these classes of drugs are discussed below.

**The final sections** address ten developing areas which could, over the next 5-7 years, significantly improve the diagnosis and treatment of Alzheimer's disease. The discussion covers issues such as why treatments that worked on the mouse models of Alzheimer's disease aren't working in humans, why we should focus on the patient and not just the disease, stem cells, combination therapy, and most importantly, the concept of "environmental enrichment," and how this could dramatically impact the patient with Alzheimer's disease.

# the future: ten findings that could make a difference in the next five to seven years

## 1. Vaccines

Vaccines became a real possibility when animal models of Alzheimer's disease were created. Researchers then designed a modified A-beta which, when it was injected into genetically engineered 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 in the plaques and an improvement in the cognitive abilities of the mice<sup>[189]</sup>. 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.)<sup>[190]</sup>

So where do we stand? New, modified A-beta vaccines have been designed that are anticipated not to cause inflammation of the brain, and are currently in clinical trials. 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 was given as a nasal spray to a mouse model of Alzheimer's disease, and was claimed to stimulate the brain's immune cells (microglia), which then became a major contributor to the "mopping up" of excess A-beta molecules, an activity that is impaired in Alzheimer's disease. Intranasal delivery promises to become a major feature of new therapeutic treatments<sup>[191]</sup>, even for administration of stem cells<sup>[192]</sup>.

In another approach, instead of giving substances that 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 reactions such as inflammation of the brain. A new experimental vaccine has been created that

targets neither A-beta nor the tau protein of the tangles, but instead targets one of the key enzymes involved in splitting the toxic A-beta from its big parent protein<sup>[193]</sup>.

Finally, a very large study was done on people who had received intravenous immunoglobulin (IVIg) treatments for immune deficiency disorders and a variety of diseases including cancer<sup>[194]</sup>. *Immunoglobulin* is the name given to the natural antibodies in our blood, produced continuously by the body to protect it against various kinds of dangerous invading substances or organisms. These people were found to have about half the risk of developing Alzheimer's disease of people who had not received the IVIg treatment. This exciting discovery has led to a number of clinical trials of IVIg as a preventative measure against Alzheimer's disease. A cautionary word, however: a recent study<sup>[195]</sup> found that if naturally occurring antibodies in blood can get across the BBB (discussed earlier with regard to head injury), which has to be defective for some reason for this to happen (as it seems to be in Alzheimer's disease), they may actually bring about an increase in A-beta inside the nerve cells. This problem is still to be resolved.

New evidence suggests that much of the damage of excess A-beta occurs at the synapses, interfering with the communication between nerve cells, as has already been discussed. It seems that the therapeutic antibodies in the vaccines first bind to the APP (the "parent" protein from which the A-beta is split off), which is located on the surface of the cells. Normally, the APP is internalized, a process that gets it into the cell interior, where the A-beta is split off, and, if it is allowed to accumulate, where it does its damage. It is now hypothesized that the antibodies accompany the APP into the cell, and there they prevent the threatening clustering of the A-beta molecules. It has even been suggested that this can restore the communication across the damaged synapse<sup>[196]</sup>. All this new understanding is, in the opinion of this writer,

*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.*

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a truly promising advance, though others are not so impressed!

While much remains to be found out, the early news from the large number of ongoing vaccine trials is giving hope that within five to seven years there could well be a vaccination therapy that could revolutionize the treatment of Alzheimer's disease.

## 2. Macrophages

The use of macrophages is another approach designed to enhance the elimination of the threatening A-beta. An exciting recent finding could dramatically influence the strategy of enhancing the elimination of A-beta from the brain<sup>[197]</sup>. The focus here is on "scavenger" cells called *macrophages*, which are made in the bone marrow. Scavenger cells do what one would expect from the name: they detect and eat up their target. The investigators discovered the chemical in the body that made these particular macrophages sense the presence of A-beta, which they then attacked and eliminated. One day, macrophages sensitized to A-beta in this way could be introduced directly into the human brain to do this exact job (at present shown only on



mouse models of Alzheimer's disease). Until recently, elimination of A-beta was assumed to be the responsibility of the brain's immune cells, microglia; however, these are impaired in the Alzheimer brain, as mentioned earlier, so introducing modified macrophages to do the job could be an excellent way to go.

### 3. Statins and secretases

Both statins and secretases are drugs that can prevent the production of the threatening A-beta. Statins are cholesterol-reducing agents that were investigated particularly because the incidence of Alzheimer's disease appeared to be less for people who were using them to lower their cholesterol levels. At first, it was assumed that the benefit of 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<sup>[198]</sup>, so here is another promising future treatment strategy. Moreover, keeping cholesterol from rising above normal levels is clearly very important in preventing the

adverse effects already described on cell membranes and the impaired responses of nerve cells to substances such as growth factors, transmitters, hormones and of course drugs<sup>[199]</sup>. However they work, statins could well prove to be a reliable approach to combating Alzheimer's disease<sup>[200]</sup>, and have even been found to reduce the risks associated with TBI<sup>[79]</sup>.

We also expect one or more successful candidates from the other main class of drugs designed to reduce the accumulation of A-beta in the brain, those that inhibit the enzymes (secretases) involved in splitting off the A-beta from the large "parent" APP protein. A recently reported drug of promise was very effective in a mouse model of Alzheimer's disease, both in reducing the numbers of plaques (implying a reduction in A-beta levels) and in improving its memory performance<sup>[201]</sup>; one appeal of this drug is that can be delivered by mouth.

### 4. Anti-diabetic drugs

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 the rest of the body, improved memory and cognition in some people, and in other studies reduced the levels of four important proteins involved in the production of A-beta, the prime therapeutic target in Alzheimer's disease research<sup>[201]</sup>.

### 5. Biomarkers

Earlier, we discussed the need for reliable biomarkers, objective tests that could help in the diagnosis of Alzheimer's disease without a total reliance on psychological examination, or on carrying out the relatively invasive procedure of lumbar puncture, which certainly offers good biomarkers. A positive outpouring of reports have described changes in various proteins in the blood of

# the future: ten findings that could make a difference in the next five to seven years



*Conditions that primarily affect the brain are now being found to affect the cells of the retina, too. The amyloid plaques discussed about the Alzheimer brain have now been found to occur in the eyes of people with Alzheimer's disease<sup>[204]</sup>. Not only that, but therapeutic approaches in animal models of Alzheimer's disease that reduced the plaque numbers in the brain did so for the retinal plaques, too<sup>[204]</sup>.*

people with Alzheimer's disease, and it seems likely that at least one of these will become a routine test within the next five years.

## 6. Of mice and men

This report will not cite the numerous recent reports of drugs that worked well in the mouse models of Alzheimer's disease, only to fail in humans. They include drugs designed to block the enzymes that split off the A-beta from the "parent" protein, APP, drugs designed to stop the individual A-beta molecules from sticking together to form the toxic oligomers discussed earlier, and vaccines. But it sticks out a mile that there have to be some important differences between mice and humans that are pertinent to this issue<sup>[202]</sup>. Unfortunately these mouse models are the best we have.

It is often suggested that the drugs worked in these mice because their level of Alzheimer's disease was equivalent to only the very earliest stages of Alzheimer's disease in

humans, earlier than the disease levels in those participating in the usual clinical drug trials. If this is true, then the drugs could at least be considered as possible treatments for those people anticipated to be detected in the newly proposed strategy for early diagnosis of Alzheimer's disease already discussed. Actually very relevant genetic changes have been found in the brain cells of the mouse models, virtually identical to those in the equivalent cells of the human Alzheimer brain, suggesting that the mouse models aren't too far from the human Alzheimer state<sup>[202A]</sup>.

A new look at the problem has come from a Japanese study<sup>[203]</sup> that draws attention to the likelihood that the adverse effects of some risk factors might be exerted only if the A-beta threat is already present for one reason or another. To produce the "combination threat," both the risk factor in question and the A-beta would have to be present in certain critical levels. If the levels of one or the other of these two were not the "correct" ones, there might not be a threat at all. Therefore the appropriate levels to constitute a threat might be quite different in mice and humans. In these studies, the threat was provided by the simultaneous presence of A-beta on the one hand and homocysteic acid on the other. (Homocysteic acid was discussed earlier.) As it happens, the threatening "combination" levels did turn out to be quite different in mice and humans. It follows that a "combination therapy," the simultaneous administration of, say, two drugs, one for A-beta and one for homocysteic acid, would need to be tailored so that it was appropriate for either humans or mice. This might explain why just transferring a successful mouse combination therapy to the human might be unsuccessful.

## 7. The eye

Nerve cells in the retina of the eye send their long nerve fibres to connect with other nerve cells in the brain, and the retinal nerve cells are regarded as part of the central nervous

system (CNS), which is the brain and the spinal cord. (The other part of the nervous system is the *peripheral nervous system*, whose cells make their connections outside the CNS, in muscles and skin especially). Not surprisingly, then, conditions that primarily affect the brain are now being found to affect the cells of the retina, too. The amyloid plaques discussed about the Alzheimer brain have now been found to occur in the eyes of people with Alzheimer's disease [204]. Not only that, but therapeutic approaches in animal models of Alzheimer's disease that reduced the plaque numbers in the brain did so for the retinal plaques, too [204].

There's more: we can't visualize sick and dying nerve cells in the living brain, but there are chemicals that, when they arrive at such cells, bind to them, and these chemicals are fluorescent—they light up with characteristic colours when light of a certain wave length (virtually invisible) shines on them. So now it will be possible to give these chemicals to people with Alzheimer's disease, shine an appropriate light into their eyes, and see if the retinal cells are dying. Also, after an Alzheimer's disease-modifying (curative) drug is administered, it will be possible to see if it has rescued the retinal cells or not! These findings suggest future revolutionary approaches to diagnosing the presence of Alzheimer's disease pathology non-invasively. They also suggest approaches to following the effectiveness of treatments in the living patient, possibly before a true dementia has developed.

## 8. Therapeutic approaches aimed at curing the patient as well as the disease

*STEM CELLS: AN APPROACH TO PROVIDING NEW NERVE CELLS TO REPLACE THOSE LOST DURING THE DISEASE PROCESS.* This section will clarify this much talked about area of research. Researchers are very excited at the prospect of replacing lost nerve cells in Alzheimer brains, by using special cells

known as stem cells, which were mentioned earlier. These immature cells occur naturally in most of the body's tissues, such as bone marrow, skin, and also the brain, and there's some evidence that the body can use them as a source of replacement cells, to be recruited whenever tissue degeneration occurs due to disease or trauma. (They're part of the body's natural repair strategy.) There is also evidence that this repair function can happen spontaneously after traumatic brain injury, and even in neurodegenerative conditions like Alzheimer's disease [205]. The aim of Alzheimer researchers is to encourage stem cell research, and in particular to devise methods for getting them into the regions of the brain where nerve cell degeneration has occurred. Stem cells are multipotent, or pluripotent, meaning that under appropriate conditions any stem cell can transform into any particular adult cell type.

There are, however, problems associated with stem cell research

### *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.

The most popular source of stem cells to date has been embryos or fetuses, in which stem cells are abundant [205A], 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 and many other countries have important limitations on stem cell research in this regard. Once a source of stem cells has been established, say from aborted fetuses, the cells are transferred to special chambers 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. What kind of adult cells they become depends on what's added to the culture medium. Experimentally, we do what the body does, expose the stem cells to

"trophic" substances (e.g., the growth factors NGF and BDNF, already mentioned). But new genetic engineering advances, allowing the insertion of genes into cells, are changing the scene dramatically. For example, even adult skin cells have been converted back into an earlier embryo-like stage (they were "reprogrammed" [206], and in other experiments adult skin cells were directly converted into nerve cells without requiring that they first revert to stem cells [207]. Studies like these are especially exciting because firstly, human fetuses wouldn't be involved, and secondly, if the cells came from the patient's own skin, they wouldn't be rejected by the immune system.

*THE CONVERTED STEM CELLS MAY NOT BE PERFECTLY NORMAL.* Some Canadian studies of stem cells that reside in normal adult skin showed that after they were removed and genetically transformed into nerve cells, they looked good, but some critically important mechanisms required for the cells to produce nerve impulses (messages) were missing—an important defect by any standards [208].

### *HOW CAN WE KNOW THAT ANY NEW NERVE CELLS IMPLANTED INTO THE BRAIN WILL SEND OUT AND RECEIVE THE CORRECT CONNECTIONS WITH OTHER NERVE CELLS IN THE BRAIN, I.E., HELP REBUILD LOST CIRCUITRY?*

We have no way at present of controlling this [208A]. The results could be threatening (or "maladaptive"). One hope, supported by some experimental findings, is that "cues" exist, even in the adult brain, that help guide newly growing nerve fibres to correct destinations as happened during the development of the brain in early life [209]. Perhaps this would lead to a restoration of normal functions, including memories, lost during the progression of the disease.

*HOW LONG BEFORE WE HAVE A VIABLE STEM CELL REPLACEMENT THERAPY?* This writer's best guess is that it will take 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

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we await this desirable result, it is encouraging to know about the other promising treatments on the horizon.

**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 is no further brain degeneration, there will still be the need to deal with the damage that has already happened. We have to cure the person as well as the disease!

Of great importance here are the growth factors such as BDNF and NGF mentioned earlier, which can stimulate nerve cells to undergo compensatory nerve sprouting, believed by many to be involved in the recovery often observed after stroke and brain trauma, for example. Unfortunately, sprouting can be impaired in aging<sup>[210]</sup>, and it may also be reduced by some of the known risk factors for Alzheimer's disease<sup>[211]</sup>. Of great relevance, the shrinkage of the brain's nerve cells and the associated cognitive decline that occurs in both rats and primates as they age, were both substantially reversed by infusion of BDNF into the brain<sup>[212]</sup>. Scientists are now implanting genetically engineered cells that make NGF or other growth factors into the brains of animal models of Alzheimer's disease and, in one study, directly into the brains of people with Alzheimer's disease<sup>[213]</sup>. Initial results show promise both for keeping nerve cells from dying and in improving cognition and memory.

All this will take quite a few years to produce the results we want. Another more immediate and quite different way of promoting brain repair involves something as simple as social interaction with others.

**Caregiving and "environmental enrichment" could promote 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 die. Nerve sprouting is induced by growth factors among which NGF and BDNF are 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" 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. 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 the person's 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 density of neurofibrillary tangles and the levels of A-beta and the amyloid deposits<sup>[214, 215]</sup>. Also, in rats whose brains were subject to an experimentally reduced blood supply that permanently impaired their cognitive functions, environmental enrichment promoted sprouting and increased connectivity between brain cells and reversed their memory defects<sup>[216]</sup>. Even in normal mice, the same kind of enrichment had similar positive effects on their brain circuitry<sup>[217]</sup>.

The caregiver, family member, or anyone else involved with the person with Alzheimer's disease could have a critical role here. We should never be put off by the absence of an immediate response from the affected person, because nerve sprouting and the subsequent making of connections with other nerve cells

can take many months. This proposal has obviously not been proven experimentally in humans, but a lot of animal research would support it, and anecdotal accounts this writer has received 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 by holding and caressing the person (without overdoing it, of course, which could cause distress to both sides). The thing to avoid at all costs is social isolation.

## 9. Animal studies offer hope that lost long-term memories may be recoverable<sup>[218]</sup>

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 on the importance of social interaction 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

*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.*

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facilitated, even in brain-damaged animals.

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.

## 10. Combination therapy: A hopeful future

Earlier mention was made of the usefulness of combining two therapeutic agents (cholinesterase inhibitors like Aricept along with memantine [Ebixa]), and of the possible need to combine different agents to attack different disease abnormalities that are present at the same time. What has yet to appear is a combination of a drug therapy along with a behavioural (e.g., cognitive) one. Perhaps one such approach will appear over the next five years. When methods are established for safely and successfully administering the growth factors we've already discussed (e.g., NGF and BDNF) to people with Alzheimer's disease, it cries out that the same people should simultaneously receive the already established exercise and cognitive therapies proven to improve their mental and physical status. All this requires is a collaborative approach between researchers working in quite different disciplines. It may take years, but it must come.



# conclusion

**THE IDEAL COMBINATION THERAPY** that could both halt the Alzheimer's disease process and restore lost functions including memory would include one or other of

- (i) the approaches to restoring brain circuitry discussed here (delivery of growth factors, delivery of stem cells and transformed skin cells, and mobilizing of stem cells already resident in the brain) with
- (ii) the appropriate disease-modifying drug treatments currently undergoing clinical trials (drugs that reduce A-beta production and those that enhance A-beta elimination, including vaccines), together with
- (iii) now-established behavioural therapies.

## RESEARCH REPORTS ON ALZHEIMER'S DISEASE

Finally, a glimpse at the encouraging numbers of research reports on Alzheimer's disease that appeared in the 8-month period from January to August, 2011. There were many more in 2010 and in preceding years.

These reports appeared in reputable clinical and basic science journals, and were all reviewed and recommended for publication by critical fellow scientists. To stay in the front line of research, scientists must keep up with these findings! As well, researchers need publications to improve their chances of obtaining funds to support their work, and to stand a fighting chance of obtaining and keeping their research positions.

The following is a listing of reports published between January and August, 2011, showing the number of reports that addressed the numbered topic. In many instances, the same publication may have addressed more than one topic.

- *Therapeutic Drugs* (almost 300)
- *Advances in diagnosis* (more than 1,000)
- *Biomarkers of Alzheimer's disease* (more than 400)
- *Brain imaging in Alzheimer's disease* (more than 500)
- *Cognitive training of Alzheimer patients* (more than 160)
- *Brain pathology (abnormalities) in Alzheimer's disease* (more than 1,500)
- *Risk factors for Alzheimer's disease* (more than 269)
- *Prevention of Alzheimer's disease* (more than 175)
- *Causes of Alzheimer's disease* (more than 850)

## A note on citations

Scientific reports customarily provide individual citations for specific findings mentioned in the text. In the reference section of this report, selected publications, commendable in their own right, have been cited additionally as a source for a number of citations that would otherwise have to be identified individually.

## LIST OF ABBREVIATIONS

<b>ADRD</b>	Alzheimer's disease and related dementias
<b>ASC</b>	Alzheimer Society of Canada
<b>BBB</b>	blood-brain barrier
<b>BDNF</b>	brain-derived neurotrophic factor
<b>CR</b>	caloric restricted (diet)
<b>CNS</b>	central nervous system
<b>CSF</b>	cerebrospinal fluid
<b>CT</b>	computed tomography
<b>FAD</b>	familial Alzheimer's disease
<b>fMRI</b>	functional MRI
<b>HRT</b>	hormone replacement therapy
<b>IVIg</b>	intravenous immunoglobulin
<b>MCI</b>	mild cognitive impairment
<b>MRI</b>	magnetic resonance imaging
<b>MRS</b>	magnetic resonance spectroscopy
<b>NGF</b>	nerve growth factor
<b>PET</b>	positron emission tomography
<b>ROS</b>	reactive oxygen species
<b>TBI</b>	traumatic brain injury
<b>UV</b>	ultraviolet

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## Alzheimer *Society* CANADA

**Alzheimer Society of Canada**

20 Eglinton Avenue West, 16th Floor

Toronto, ON M4R 1K8

Tel.: 416-488-8772

Email: [research@alzheimer.ca](mailto:research@alzheimer.ca) | [www.alzheimer.ca](http://www.alzheimer.ca)

Facebook: [www.facebook.com/AlzheimerSociety](http://www.facebook.com/AlzheimerSociety) | Twitter: [www.twitter.com/AlzSociety](http://www.twitter.com/AlzSociety)

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