



2008 Research Report Summary

A synopsis of new Alzheimer's Disease Research Information

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Alzheimer *Society*

Research in Alzheimer's disease is constantly progressing and this summary represents the new and/or changed information and advances in research since the 2006 edition of *A Report on Alzheimer's Disease and Current Research*. This synopsis is intended as a companion piece to the report, providing the most up-to-date information possible at the time of printing. Please refer to the entire report, which presents an overview of Alzheimer's disease and the most promising research investigating new treatments and the search for a cure, for more details. A full updated and revised report will be available online at www.alzheimer.ca by April 2008).

Risk Factors

Genetic risk factors

In addition to the genes responsible for Familial Alzheimer's disease and the apoE4 gene, more than a dozen gene variants have been identified that occur in people with Alzheimer's disease to a greater extent than in non-Alzheimer's people. Researchers are especially interested in the evidence that some variant genes (like the recently discovered SORL1 gene) lead to a situation in the nerve cells that favours the production of the potentially dangerous A-beta protein (also called beta amyloid). Further research on these suspect genes could produce results that help chemists design drugs that would lessen the production of this threatening protein. In addition, a newly identified gene, GAB2, in its healthy form appears to protect the brain from developing tangles, but in the modified form found in the Alzheimer brain seems to promote the development of tangles inside nerve cells.

Diabetes

It has been known for some years that type 2 (adult) diabetes is a risk factor for Alzheimer's disease. New research techniques and brain imaging have now revealed that the Alzheimer brain is itself in a sort of diabetic state (independently of the rest of the body), and it has even been suggested that Alzheimer's disease be called "type 3 diabetes" even though the affected person may not be diabetic in the ordinary sense. It's now known that in type 2 diabetic people, the toxic protein implicated in plaques

(the beta amyloid, or A-beta) may be present in the pancreas (the organ that normally produces insulin), strengthening the suspected link between type 2 diabetes and Alzheimer's disease. Researchers are testing anti-diabetic drugs (like those that are beginning to look promising for the conventional type 2 diabetes) in cases of Alzheimer's disease, and here too there are indications of beneficial effects on brain functions like memory and cognition.

Strokes and mini strokes

It is now known that both strokes and traumatic brain injury cause increases in enzymes called caspases, which through a series of biochemical steps then allow other enzymes called BACE to build up in the brain. Increased BACE activity is partly responsible for the excessive formation of the toxic A-beta protein in the Alzheimer brain. Although this news is hardly pleasing, it does help explain why strokes and mini strokes are risk factors, and it does help guide researchers in their search for treatments.

Reducing The Risk

Healthy Eating

Much is known about how healthy eating can help reduce the risk of Alzheimer's disease and this area continues to be studied. New knowledge suggests that moderate intake of red wine may also reduce the likelihood of developing Alzheimer's disease. Similarly, curcumin, a spice used in curries, has been especially implicated in the lower than average incidence of Alzheimer's disease in curry-eating populations, and research is actively identifying and testing drugs that mimic the active ingredients in curcumin.

Brain Changes Occurring In Alzheimer's Disease

Many researchers believe that the threatening A-beta molecules not only make the nerve cells sick, but they somehow promote the development of tangles, and it is probably these that actually kill the nerve cells. New research is suggesting that a very early event is the entry of the accumulating A-beta molecules into the nerve cells where the A-beta interacts with and modifies the tau molecules that are the basis of the tangles. The resultant

complex is toxic, and is probably responsible for the earliest degenerative changes in the nerve cells and synapses.

Diagnosis of Alzheimer's Disease

Brain Imaging

In some instances brain imaging will be used as a contributor to the diagnosis of Alzheimer's disease. Magnetic resonance imaging (MRI) and computed tomography (CT) give valuable information about the shape and volume of brain regions. We are now seeing that positron emission tomography (PET) and functional MRI (Fmri) reveal how well cells in various brain regions are actively using the sugar and oxygen brought by the brain's blood supply, functions which significantly reduce in Alzheimer's disease. In addition, exciting new imaging techniques are emerging that address the problem of what's happening in regard to plaques during life rather than finding this out post mortem. Special tracer compounds, chemicals that show up in the imaging process, are injected into the blood circulation and thereby reach the brain. These chemicals attach to the A-beta proteins that form the plaques, which are then visualized without any surgery or exposure of the brain. One day this technique could become widely available, assisting not only in the diagnosis of Alzheimer's disease, but also helping to show whether treatments are working, since these treatments would be expected to significantly reduce the number of plaques.

Early diagnosis by measuring chemical levels in tissues outside the brain

It has long been hoped that biological markers for Alzheimer's disease would appear in various tissues that could be more easily accessed and studied than the brain itself. New findings are offering hope that early diagnosis could be considerably assisted by such biological markers. Recent reports described two such in the skin of people with Alzheimer's disease, firstly an abnormal inflammatory chemical response that is easy to detect, and secondly, the presence of abnormal levels of a number of proteins.

Revised diagnostic testing

A revised diagnostic testing protocol has been recently proposed which includes imaging evidence for shrinkage of key brain regions, evidence of reduced glucose utilization in the brain, the presence in the cerebrospinal fluid (the fluid

which bathes the brain and spinal cord), abnormal levels of A-beta, evidence of the existence of a genetic mutation for Alzheimer's disease within the immediate family, and of course unambiguous indications of dementia. Discussion continues on whether this newly proposed set of criteria should become the universal standard.

Drug Treatments

Vaccines

Vaccines became a real possibility when animal models of the disease were created and when the first vaccine proved to successfully eliminate the toxic A-beta from their brains. Human trials were immediately undertaken, but within two years they were discontinued because brain inflammation occurred in a few cases. New vaccines anticipated not to cause inflammation of the brain are very actively being designed, and at least three are already in early clinical trials. In one new approach, the vaccine is given as a nasal spray, which is claimed to stimulate the brain's immune cells which then will mop up the excess A-beta molecules. In another approach, instead of giving substances which will stimulate the production of antibodies (active immunization), already manufactured antibodies are provided directly (passive immunization). Finally a new experimental vaccine has been created which targets one of the key enzymes involved in splitting the toxic A-beta from its big parent protein. While much remains to be discovered, the early news gives hope that within five to seven years, there could well be a vaccination therapy that could revolutionize the treatment of Alzheimer's disease.

Alzhemed

Alzhemed™, is part of a new class of drugs that work by blocking the aggregation of individual A-beta molecules into the small clumps ("oligomers") which are the real cause of the toxic actions of A-beta on nerve cells. However, Alzhemed's initial promise was not supported in expanded clinical trials, and it has now been discontinued. New findings suggest that drugs like Alzhemed may be inherently flawed because they themselves form clumps that cannot get into the brain to achieve the original purpose of preventing oligomer formation. However, this is not yet a firmly established finding.

Stem Cells

A persisting problem in stem cell research has been how to obtain the substantial number of stem cells needed for research. Two recent research reports have cast new light on the situation. Using a 'retrovirus' as an infecting agent, certain molecules known as 'transcription' factors were introduced into fully developed human skin cells. Genes were activated that converted adult skin cells back into an earlier and more primitive state, into cells in fact that closely resembled normal embryo-derived stem cells. But it's now suspected that the resemblance may not always be close enough. The excitement generated by these reports was not just because of the discovery of how to transform normal adult cells into stem cells, but because of the implication that stem cells could now be obtained without the involvement of human fetuses. While there are some big pluses to using stem cells as potential replacement cells, there are also drawbacks which need further study. Likely it will be decades at the very least before we have a viable stem cell replacement therapy.

Animal Studies Offer Hope That Lost Long-Term Memories May Be Recoverable

In this work two genes were studied in mice. One gene, when activated by appropriate drugs, caused nerve cells to

die just as in Alzheimer's disease, and as in Alzheimer's disease, long-term memory was lost. The first truly exciting result was that when put into an "enriched environment", the long-term memory eventually reappeared, despite the loss of nerve cells. It has been known for some time that animals living in an enriched environment, in which they are exposed to many more opportunities for play and exploration, develop many more connections between nerve cells in the brain, and they are able to learn more quickly. The second gene the researchers studied is involved in the formation of long-term memories (probably by sprouting new connections). Unexpectedly, a protein that occurs normally in the body was found to suppress this gene, so interfering with long-term memory production. The researchers were able to oppose the action of this suppressor protein with another drug, and in these mice long-term memory formation was facilitated, even in brain damaged animals. The key message from these studies is that long-term memories may not be totally lost in Alzheimer's disease, but may have become inaccessible. New research is focusing on how to stimulate the production of new connections among surviving nerve cells so as to access these memories. Socialisation and exposure to an enriched environment are two promising ways to help achieve this objective.

This synopsis provides a summary of the new and/or changed information since the publishing of the Nov. 2006 version of A Report on Alzheimer's Disease and Current Research by Dr. Jack Diamond, Scientific Director of the Alzheimer Society of Canada.

For more information on Alzheimer's disease and Alzheimer's disease research, please visit www.alzheimer.ca.

Alzheimer Society

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