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Alzheimer's Disease - Part II Causes and Treatments

By: James L. Holly, MD

Two significant abnormalities occur in brains of people affected by Alzheimer's:

1. Twisted nerve cell fibers, known as neurofibrillary tangles and
2. A sticky protein called beta amyloid.

Beta amyloid is a sticky a protein, which forms plaques in the brain. These plaques are found outside the nerve cells surrounded by the debris of dying neurons. High levels of beta amyloid are associated with reduced levels of acetylcholine, a chemical messenger, which is essential for memory and learning, and is progressively destroyed in Alzheimer's patients.

Some researchers think that beta amyloid may break into fragments that release unstable chemicals in the body that, through a process called oxidation, bind to other molecules and cause damage to the brain. Oxidation is known to play a role in many serious diseases, including coronary artery disease and cancers, and experts believe it may also contribute to Alzheimer's. One of its effects is the so-called inflammatory response, in which the immune system overproduces factors normally intended to fight harmful agents, but in excess, they can actually injure the body's own cells.

Genetic Research

In late-onset Alzheimer's Disease (after age 85), the major target in genetic research has been apolipoprotein E (ApoE), which plays a role in the movement and distribution of cholesterol for repairing nerve cells during development and after injury. The gene for ApoE comes in three major types: ApoE2, ApoE3, and ApoE4; people inherit a copy of one type from each parent. Studies have reported greatest deposits of beta amyloid in people with ApoE4, fewer in ApoE3, and lowest in those with ApoE2. Some research indicates that ApoE3 and ApoE4 may induce changes in beta amyloid that trigger an inflammatory response in the brain. ApoE2 appears, on the other hand, to have protective qualities.

Alzheimer's disease is not inevitable, however, even in people with two copies of the ApoE4 gene. Reports vary widely in estimating the extent of risk. In people without

ApoE4, estimates for the risk of developing Alzheimer's by age 85 range from 9% to 20%; in those with one copy of the gene, the risk is between 25% and 60%; and in people with two copies, the risk ranges from 50% to 90%.

The good news is that only 2% of the population carry two copies of the ApoE4 gene. Some research indicates that a specific variation of the ApoE4 gene may be the primary culprit in the development of Alzheimer's, which would explain why many people with ApoE4 exhibit no signs of Alzheimer's. A number of studies also indicate that ApoE4 gene occurs in about 20% of cases of vascular dementia, which is dementia caused by blockage in blood vessels to the brain. ApoE4 has been studied for years as a risk factor for coronary artery disease, and some studies have found a higher risk for atherosclerosis in people with Alzheimer's disease who also carry two copies of the ApoE4 genotype.

Research into the causes of Alzheimer's Disease also includes investigation into the following areas:

Virus and Bacteria -- No evidence exists that Alzheimer's is transmittable, but a possible scenario is a genetic susceptibility coupled with a breakdown of the immunologic system that leaves a person vulnerable to slow acting viruses.
Metals -- In spite of some early concern that aluminum may have some role in Alzheimer's, studies have found no relationship between the development of Alzheimer's and exposure to aluminum in cooking, occupational work, or drinking water.
Electromagnetic Fields -- Some, but not all, studies on people exposed to intense electromagnetic fields have reported a higher incidence of Alzheimer's. Some researchers believe that magnetic fields may interfere with the concentration of calcium inside cells, and others believe that they may increase production of beta amyloid.
Head Injury -- Injury to the head can accelerate the development of Alzheimer's in people who are already susceptible to it.
Childhood Malnutrition and Vitamin Deficiencies -- According to one study, poor nutrition in childhood may render the brain more susceptible to mental impairments later in life, including Alzheimer's disease.

No single cause of Alzheimer's has been identified, but research is promising. Hopefully, soon there will be a clear understanding of the cause, or more likely, the causes of Alzheimer's because the development of a cure and/or treatment depends upon that knowledge.

Treatment of Alzheimer's

Acetylcholine Drugs

At present, most drugs being used to treat Alzheimer's or are under investigation are aimed at slowing progression; there is no cure. In fact, the improvements from some of these drugs that are considered significant in studies may not even be noticed by the patients or their families, but they may delay the need for admission to nursing homes.

Cognex and Aricept

Cognex and Aricept are designed to increase the amount of acetylcholine in the brain. Both drugs have modest benefits; patients taking either drug usually show improvement in functioning and behavior. Typical side effects of both drugs include nausea and diarrhea. Cognex needs to be taken four times a day, but Aricept only needs to be taken once a day. The benefits of these and other drugs that protect the cholinergic system are far from dramatic, however; about half of patients with mild to moderate disease show slight improvement, and when they go off the drugs the deterioration continues.

Many experts have reservations about drugs that affect the cholinergic system, because such drugs, at best, only slow progression but will never cure the disease.

Anti-Inflammatory Drugs

Anti-inflammatory Drugs

Because the inflammatory process may play a role in Alzheimer's, a number of anti-inflammatory drugs are being studied. Nonsteroidal anti-inflammatory drugs (NSAIDs), which include aspirin and ibuprofen, are under intense scrutiny. Corticosteroids are the most often-prescribed anti-inflammatory drugs, but long-term use may actually cause memory loss and they do not appear to effect prostaglandins, substances that appear to be factors in the development of Alzheimer's and which are targets of NSAIDs. Other anti-inflammatory agents being considered include corticotropin releasing factor (CRF), thalidomide, and tenidap.

Other Drugs

Estrogen and Other Hormones - Estrogen replacement therapy appears to slow progression and even prevent Alzheimer's disease, causing interest in possible other hormone therapies.

Antioxidants - One study found that two daily doses of vitamin E (1000 IU each dose) or of selegiline (Eldepryl) (5 mg each) delayed the progression of the disease or its symptoms. These two agents appeared to provide equal benefits, but combining them did not add any advantage.

Ginkgo Biloba - A common herb that appears to increase blood flow to the brain and has antioxidant properties. New studies have suggested that ginkgo biloba may slightly improve the memory of Alzheimer's patients, although it is not clear if the improvement is significant.

Nicotine - Nicotine acts on receptors in the cholinergic system in the brain that are depleted by the Alzheimer's disease process and some studies have suggested that nicotine may protect nerve cells and help prevent the formation of beta amyloid. Although nicotine itself, unlike smoking, does not cause cancer, it has widespread side effects. Researchers are investigating nicotine-like drugs that may protect nerve cells

without causing as many side effects. The effects of smoking itself on Alzheimer's have been unclear, although a recent one reported that the risk of dementia is significantly increased in smokers. In any case, smoking is never recommended for either prevention or treatment.

The Future - A vaccine for Alzheimer's

The first tests in people of a vaccine that may slow or prevent the devastation of Alzheimer's disease have so far shown that the approach is safe. However, it's still too early to gauge whether the vaccine actually works. Newly reported animal tests add to the cautious optimism about the new vaccine strategy. In mice genetically engineered to develop brain lesions similar to those seen in Alzheimer's disease, the vaccine averted expected declines in certain memory and learning skills. In 1999, Dale Schenk of Elan Pharmaceuticals in South San Francisco reported that simply injecting such mice with a protein fragment called beta-amyloid keeps naturally-occurring amyloid from accumulating in the brains of the rodents and even eliminates preexisting amyloid deposits known as plaques.

Many scientists believe that the abnormal buildup of amyloid brings about Alzheimer's disease, and Elan's vaccine offers the first possible treatment for this apparent root cause of the illness. The vaccine elicits antibodies that bind to beta-amyloid. While the antibodies generally circulate in the bloodstream, some apparently leak across the blood brain barrier. Once in the brain, the antibodies seem to mark amyloid plaques for clearance by microglia, which are immune cells that patrol the brain.

The future is cautiously hopeful for a treatment for Alzheimer's. Without doubt, the best way to face the threat of Alzheimer's is by keeping yourself physically, mentally, emotionally and spiritually fit. Reading rather than passively watching TV or movies has been suggested as beneficial in forestalling Alzheimer's. Good nutrition with high vegetable and fruit content rather than heavy dependence upon animal protein help prevent the build up of toxic substances in the body. Exercises keeps the cardiovascular system working optimally.

Until there is a cure or a treatment for Alzheimer's these are the most important things you can do.

Remember, it's your life and it's your health.