HEALTH AND STRESS

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STRESS AND ALZHEIMER'S SOME SURPRISING LINKS

KEYWORDS: Senior moments, adult attention deficit disorder, risk vs. deterministic genes, APOE4, beta-amyloid, neurofibrillary tangles, CRP, homocysteine, smoking, statins, glial cells, *Alzheimier's Solved*, hippocampal atrophy, Alzheimer animal studies, aging and telomerase, corticotropin releasing factor receptors, estrogen, caregiver stress,

Alzheimer's is a devastating disease, not only for patients, but family members who are often their caregivers. Since its causes are unknown, there are no effective preventive measures, nor are there any therapies that can significantly delay its inevitable and progressively debilitating course.

Also Included In This Issue

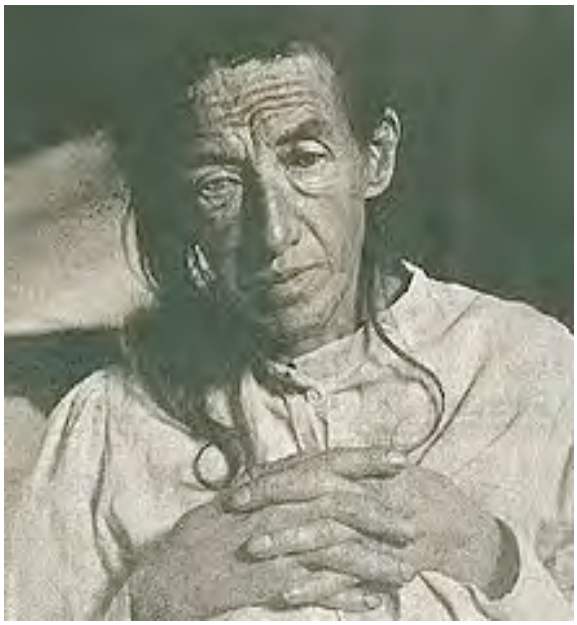
The disease was first described in 1906 by the German neuropathologist and psychiatrist, Alois Alzheimer, who had observed a 51-year old patient with loss of memory for recent events and strange behavioral symptoms usually seen only in much older individuals. Over the next five years she deteriorated and died. At autopsy, Alzheimer studied her brain using special staining techniques that revealed the hallmark amyloid plaques and neurofibrillary tangles.

Loss of short-term memory is frequently the first indication, usually manifested by forgetting names or something that happened the previous day. There may be difficulty in understanding conversations or in making sense out of what is seen or read. This can occur intermittently over months and years, during which the person is increasingly aware of the problem. As memory and reasoning become more impaired, there is a loss of interest in previously enjoyable activities and a change in behavior and personality. Unpredictable cycles of apathy and aggression and lack of social and sexual inhibitions can occur. Even in later stages there may be transient episodes of lucidity and awareness of what is happening, until the inescapable state of complete helplessness and inability to communicate becomes permanent.

How Can You Determine If You Have Or Will Develop Alzheimer's?

Alzheimer's occurs most often in the elderly and affects 20% of everyone 80 or older. Multiple small strokes can also cause senile dementia due to loss of brain cells. Senility associated with age related arteriosclerosis may exhibit similar symptoms, as can alcoholism, certain drugs and depression. Presenile dementia is sometimes used to distinguish people that develop signs and symptoms of Alzheimer's in their late forties or early fifties.

Early diagnosis can be difficult in such patients, since subtle abnormalities in behavior vary, occur intermittently and erratically, and can mimic those seen in other neurodegenerative disorders like Parkinson's and Pick's disease. Rita Hayworth is a famous example, since her progressive loss of memory and inability to remember lines in movie scripts was, for many years, attributed to her alcoholism. And since she was a celebrated movie star, others attended to her makeup and wardrobe, so she hardly resembled Alois Alzheimer's first patient, Auguste Deter, shown to the right, who died at age 56, five years after she was first seen.



While loss of memory for recent events is often the first symptom, this can also be a normal consequence of aging. Elderly people frequently remember the names and faces of grade school friends, but not someone they recently met, or what they had for dinner the night before. This age related change is a daily nuisance for most senior citizens, who have difficulty remembering the names of familiar people and places, where they left their glasses and keys, or something important they forgot to get at a store, even when it was their top priority. Many become so concerned that, "I think I am getting Alzheimer's" has become a common complaint in this most rapidly growing segment of the population.

How Common Is Minimal Cognitive Interference? How Dangerous Is It?

We are increasingly seeing these identical symptoms not only in healthy middle-aged individuals, but those in their forties and late thirties, where it is referred to as MCI (Minimal Cognitive Interference). This is defined as minor and intermittent memory lapses that do not interfere with life. A nationwide survey of physicians was conducted to determine how pervasive MCI was, who was most likely to be affected, what

they thought were its causes or future consequences, and what suggestions they had with respect to treatment and prevention. It revealed that:

- **Four out of five doctors reported that baby boomers as young as 35 had complained of significant memory and concentration problems that were usually seen only in the elderly.**
- **Nine out of ten emphasized that most patients do not discuss such complaints unless specifically asked.**
- Three out of four expected MCI complaints to increase in the next decade.
- **The leading cause of MCI was increased stress from work or personal problems (86%),** followed by natural aging and diminished blood supply to the brain, taking certain prescription drugs and not getting adequate amounts of sleep.
- Treatment recommendations most often included reducing stress, exercising more, and developing better sleeping habits. Doctors were three times more likely to use vitamins and herbal products than drugs, and six times more apt to suggest such supplements rather than referring patients to a psychiatrist, psychologist, neurologist or other specialist.

What was particularly disturbing about the survey results were how widespread mild cognitive disturbances had become in middle-aged and younger healthy individuals and how frequently this was not reported. No specific demographic groups were at particular risk, although there was a slight increase in men over women, white collar vs. blue collar workers and single people compared to married controls. Other than recommending lifestyle changes that are notoriously difficult to implement and provide erratic benefits, there seemed to be few ways to prevent or treat MCI. Equally troubling was the inability to determine if MCI might be a precursor of Alzheimer's or some other type of senile dementia. Is it the frequency, severity, nature of symptoms or some combination of these that is most important in forecasting the future? Are there genetic or other tests that can improve the accuracy of predictions?

It is impossible to answer such questions without establishing a definition of MCI that the scientific community will agree on, and which will allow researchers to rate its severity. The current MCI diagnostic criteria are:

- an individual’s report of his or her own memory problems, preferably confirmed by another person
- greater-than-normal impaired memory that can be measured by using validated standard memory assessment tests
- retention of normal general thinking and reasoning skills
- the ability to perform normal daily activities

But rather than providing clear answers, these mild cognitive impairment specifications tend to raise more questions, such as "What is normal?" Does normal vary with age, gender, race, or occupation? How much difficulty in

remembering things is so excessive that it is abnormal? When does the degree of memory deficit become so severe that it represents early dementia? How hard should one look for the presence of other subtle deficiencies in thinking and reasoning? How can these be quantified, and what is their relative importance in determining the degree of MCI or the likelihood that it will progress to Alzheimer's at a more rapid rate?

Let's be honest. Almost everyone reading this has experienced the irritating inability to remember the name of a very familiar friend, movie, TV show, famous celebrity or something else that is on "the tip of the tongue" but has suddenly vanished. This is usually followed by several frustrating minutes of going through the alphabet, trying to visualize what you are searching for, or asking others for assistance, without success. In many instances, after you have moved on to something else that is entirely unrelated, the answer will mysteriously and suddenly pop into your head as if nothing had happened. Such "senior moments" are apt to become more frequent as well as more embarrassing as we grow older, as illustrated by the following:

> An elderly couple had dinner at a friend's house. After eating, the wives went into the kitchen and their husbands began talking. One said, "Last night we went out to a new restaurant and all the food was superb. I would recommend it very highly." His friend asked "What's the name of the restaurant and what did you have to eat.?" The first man knits his brow in obvious concentration, and after a minute or two, asks "Aahh, What is the name of that red flower you give to someone you love?" His friend replies, "A Carnation??" "No. No. The other one" the man says. His friend offers another suggestion, "The Poppy?" "Nahhhh, growls the man. You know the one that is red and has thorns." His friend said, "Do you mean a rose?" "Yes, Yes that's it. Thank you!" the first man says. He then turns toward the kitchen and yells, "Rose, what's the name of that restaurant we went to last night?

Many people also experience difficulties in focusing on what they have to do that are disregarded, since they occur so frequently they are considered normal. This increased impulsivity, failure to concentrate and flight of mind can resemble adult ADD and ADHD, as in this diary.

> I decide to water my garden. As I turn on the hose in the driveway, I look over at my car and decide my car needs washing. As I start toward the garage, I notice that there is mail on the porch table that I brought up from the mailbox earlier. I decide to go through the mail before I wash the car. I lay my car keys down on the table, put the junk mail in the garbage can under the table, and notice that the can is full. So, I decide to put the bills back on the table and take out the garbage first. But then I think, since I'm going to be near the mailbox when I take out the garbage anyway, I may as well pay the bills first. I take my checkbook off the table, and see that there is only 1 check left. My extra checks are in my desk in the study, so I go inside the house to my desk where I find the can of Coke that I had been drinking. I'm going to look for my checks, but first I need to push the Coke aside so that I don't accidentally knock it over. I see that the Coke is getting warm, and I decide I should put it in the refrigerator to keep it cold. As I head toward the

> kitchen with the Coke, a vase of flowers on the counter catches my eye--they need to be watered. I set the Coke down on the counter, and I discover my reading glasses that I've been searching for all morning. I decide I better put them back on my desk, but first I'm going to water the flowers. I set the glasses back down on the counter, fill a container with water and suddenly I spot the TV remote. Someone left it on the kitchen table. I realize that tonight when we go to watch TV, I will be looking for the remote, but I won't remember that it's on the kitchen table, so I decide to put it back in the den where it belongs, but first I'll water the flowers. I pour some water in the flowers, but quite a bit of it spills on the floor. So, I set the remote back down on the table, get some towels and wipe up the spill. Then, I head down the hall trying to remember what I was planning to do. At the end of the day: the car isn't washed; the bills aren't paid; there is a warm can of Coke sitting on the counter; the flowers don't have enough water; there is still only 1 check in my check book; I can't find the remote; I can't find my glasses; and I don't remember what I did with the car keys. — Then, when I try to figure out why nothing got done today. I'm really baffled, because I know I was busy all day long, and I'm really tired. **I realize this is a serious problem, and I'll try to get some help for it, but first I'll check my e-mail**.

Difficulties in concentration can also cause typographical errors, dialing the wrong numbers, or trying to use your TV remote control to answer phone calls. Minimal cognitive interference can surface with varied symptoms, but when the predominant feature is memory loss, other symptoms and signs of Alzheimer's seem more likely to develop. Some studies suggest that this progression occurs at rates of 10% to 15% a year over an average of six years before the diagnosis is made. Like Alzheimer's, MCI also increases with age (19.2% for ages 65-74, 27.6% for ages 75-84, and 38% for 85 years and older). Unfortunately, there is no effective treatment for either disorder, nor is there anything that will significantly prevent or delay their appearance. There is evidence that MCI patients who present with other cognitive deficits, such as an inability to concentrate, are prone to develop different neurodegenerative disorders that also result in senile dementia, like Pick's and Parkinson's disease. What most people want to know is whether their occasional loss of memory or difficulty in concentration is harmless, or a harbinger of future progressive and irreversible senility.

It is currently impossible to determine if MCI is benign, or to accurately diagnose Alzheimer's in its early stages. A strong family history increases risk, especially if you have certain genes, although other genes may lower risk. The diagnosis of Alzheimer's depends on finding telltale amyloid deposits and neurofibrillary tangles of tau protein in brain tissue. Abnormal cerebrospinal fluid levels of amyloid and tau protein are seen in up to 90% of Alzheimer's patients and can precede any symptoms of dementia by 10 or more years. However they are also present in 72% of people with MCI and 36% of healthy controls that never develop the disease. There are also several neuroimaging biomarkers seen in advanced Alzheimer's but these

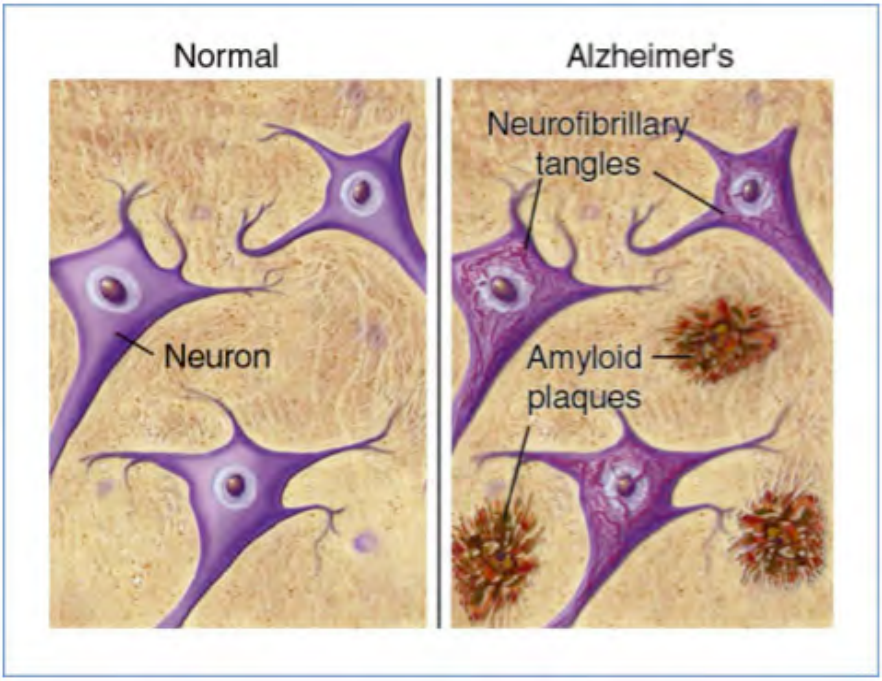
vary for different locations and are too inconsistent to be diagnostic at present. Smoking and repeated head trauma have been implicated, and while MCI is slightly more frequent in males and there are no racial or ethnic differences, more women than men develop Alzheimer's, and it is more common in Latinos and African-Americans than whites.

The fact is, that with one exception, we can't predict whether Alzheimer's will develop with any degree of certainty. **And if there were a testing procedure with 100% guaranteed accuracy, would you take it if you knew there was absolutely nothing you could do to delay the onset or minimize the devastating effects of this disease?** While your initial response might be that you would want to know as much as possible about your future, what would you do differently, other than to make sure your affairs and end of life instructions were in order? Weigh that benefit against spending the rest of your days with a sword of Damocles hanging over your head, never knowing when or how it will strike, powerless to do anything to prevent it, and dealing with family and friends who may be aware of your impending senility and doom — and then think about your answer.

What Are The Roles Of Genes, Amyloid, Tau, Inflammation And Cholesterol?

Relatively little is known about the cause or causes of Alzheimer's save for the contribution of heredity. Studies in twins suggest that 60% to 80% of patients inherit the disease and a variety of genes have been implicated. There are two types of genes that can influence the subsequent appearance of a disease – risk genes and deterministic genes - and both categories have been found in Alzheimer's. Risk genes increase the likelihood but not the certainty of developing a disease because although they are often associated with it, this does not mean they cause it. Everyone inherits a copy of some form of the apolipoprotein E (APOE) gene from each parent, but APOE4 has the strongest influence. People with one APOE4 copy are at 25%-60% risk of having Alzheimer's by age 85, which rises to 50%- 90% if two copies are inherited. Those with no APOE4 gene are at 15% risk; APOE3 has no significance; and having APOE2 actually appears to provide protection. **Deterministic genes guarantee that anyone who inherits them will develop Alzheimer's,** and three have been identified; amyloid precursor protein (APP), presenilin-1 (PS-1) and presenilin-2 (PS-2). People with any of these usually develop Alzheimer's by the time they are in their 50s and even 30's, and have a family history of others that have suffered a similar fate. However, this "familial Alzheimer's" occurs in only a few hundred families worldwide and accounts for less than 5% of all cases.

The definitive diagnosis of Alzheimer's has changed little since it was first described over 100 years ago. It still requires microscopic examination of brain tissue to demonstrate the two key components described below.



AMYLOID is a general term for fragments of a protein normally produced in the body. Beta-amyloid is a fragment snipped from a protein called amyloid precursor protein (APP). In a healthy brain, these fragments would be broken down and eliminated. In Alzheimer's, the sticky beta-amyloid fragments join and accumulate to form hard plaques that are insoluble.

NEUROFIBRILLARY TANGLES are insoluble twisted fibers inside brain cells made of tau protein. These fibers are part of structures called microtubule that transport nutrients from one part of the cell to another. Since tau is abnormal in Alzheimer's, the microtubules collapse and transport is blocked.

Amyloid plaque is deposited between neurons and is easier to detect than neurofibrillary tangles that are inside these nerve cells and require a silver stain to make them more visible. The relationship between beta-amyloid and neurofibrillary tau tangles is not known since there can be almost a complete absence of either one wherever you look, and they are not always found together. What causes increased amyloid deposits is also not clear. Some authorities believe that their buildup is due to increased production, while others suggest it results from a breakdown in mechanisms that normally promote removal. Neurofibrillary tangles made of tau protein are another enigma. As noted, tau is normally a building block and stabilizer of the molecular straws (microtubules) that transport essential substances. In Alzheimer's, tau becomes abnormal due to increased phosphorylation and the protein strands stick together like cold pasta. Although amyloid plaque is usually the earliest abnormality, tau tangles sometimes form first in early onset disease. As a result, some have suggested that plaque might be a therapeutic response, like a scab, rather than a cause of Alzheimer's.

It has been proposed that low-grade inflammation is the basic mechanism responsible for the development of Alzheimer's. Amyloid can cause inflammation, as do *Chlamydia pneumoniae*, herpes viruses and other microorganisms that have been implicated in causing Alzheimer's. Such chronic but asymptomatic infections also increase amyloid production, and HIV induces the deposition of the same type of beta-amyloid seen in Alzheimer's. Risk factors such as hypertension, elevated cholesterol, and diabetes are the same as those for coronary atherosclerosis, which is now

believed to be due to chronic inflammation rather than elevated cholesterol. And autopsy studies on coronary disease patients have also demonstrated increased amyloid deposits and neurofibrillary tangles, even when there is no history of memory difficulties or other mental problems. This association may be due to the fact that both disorders are seen more frequently in patients with the same APOE4 gene. There is no evidence that these shared risk factors have any causal effects, nor are they consistent. For example, while cigarettes increase risk of coronary disease as well as MCI and memory loss, some studies show that smoking significantly lowers the likelihood of developing Alzheimer's and Parkinson's disease. CRP, the most widely used measure of inflammation and a powerful risk factor for heart disease, has little bearing on Alzheimer's and is not elevated in patients with impaired memory, its prime precursor and symptom. In contrast, a Framingham study found that subjects with the highest concentrations of cytokines that trigger inflammation were more than twice as likely to develop Alzheimer's disease as those with the lowest levels. This suggests that there may be varied types of provocative processes that we lump together as inflammation, but which are associated with different diseases.

High blood homocysteine, which promotes inflammation and is a powerful risk factor for coronary disease and stroke, was also tied to Alzheimer's in another Framingham study of 935 carefully selected subjects. Despite an average age of 76, none had any difficulties with memory, concentration or thinking and appeared mentally and emotionally fit. After 8 years, 111 had developed some form of dementia, including 83 that were diagnosed as having Alzheimer's. In addition to cholesterol, glucose and other chemicals, homocysteine was measured and was found to be elevated (over 15) in 30% of participants on entry into the study. Researchers reported that those with high levels were nearly twice as likely as age and sex matched controls to develop dementia, including Alzheimer's. But this association does not prove that homocysteine causes Alzheimer's, since supplementation with folate and other B-complex vitamins that lower elevated homocysteine to normal levels has not been shown to provide any prophylactic or therapeutic rewards. Similarly, if what we call "inflammation" per se is the culprit, why doesn't aspirin and other anti-inflammatory drugs provide any benefits? Lead, mercury from dental fillings, and aluminum from pots and pans, particularly if cooking is done with fluoridated water, have also been incriminated. Conversely, there are claims that consuming more fish (brain food), fruits and vegetables rich in antioxidants, alcohol (particularly red wine), olive oil, curry etc. help prevent Alzheimer's, but there is scant scientific evidence to support this. The same holds true for a host of supplements containing Co-Q10, resveratrol, *Ginko biloba*, *Ginseng panax*, huperzine, omega 3 fatty acids, kava kava, DHEA, *Rhodiola rosea* and other adaptogenic herbs, various vitamins, and numerous combinations of these.

The role of cholesterol is particularly controversial. One study that followed almost 10,000 people for four decades found that those with high or even borderline high total cholesterol in their 40s were much more likely to develop Alzheimer's years later. Participants with cholesterol levels 240 or more were at 66% increased risk compared to 52% for those in the range of 200 to 239. A low HDL, which increases risk for heart disease, also predisposed to Alzheimer's in a study of 1,130 elderly residents of northern Manhattan. Those with HDLs less than 55 on entry were 40% more likely to develop Alzheimer's over the next four years than controls with higher values. Researchers cited evidence that HDL can clear amyloid deposits in the brain, and that low HDL increases risk for stroke, which also increases Alzheimer's risk. It is much more likely that these associations are due to inherited influences, since there was a preponderance of African Americans and Hispanics, and both of these groups have higher rates of Alzheimer's. Other studies have failed to find any such effect of HDL in whites, and one showed that Japanese-American men with higher HDLs were more likely to have amyloid deposits and neurofibrillary tangles in their brains. Since statins lower cholesterol, it is no surprise that administering them has been recommended, especially since early reports claimed they reduced risk 70% or more. However, there is no proof that statins, which can cause memory loss as well as amnesia, are effective in preventing, delaying or treating Alzheimer's. As with coronary heart disease, any putative benefits are much more apt to be due to reduced inflammation or clotting tendencies.

Indeed, the preponderance of evidence suggests that **high cholesterol is associated with a delay in the development of age related mental deficits.** Support comes from a Framingham study of almost 1,800 men and women with no history of dementia or stroke who were followed for 16 to 18 years. Cholesterol was checked biennially and tests to measure memory, concentration, reasoning and other cognitive functions were administered at onset and every 4 to 6 years. At the end of the surveillance period, those with cholesterols over 240 performed much better on all these cognitive assessments than others with levels under 200. However, cholesterol is too large a molecule to pass through the blood brain barrier, and so are the LDL and HDL lipopoproteins that carry cholesterol. Thus, it seems unlikely that blood levels of lipids have any significant effect on the brain and they are statistical **risk markers** rather than causative **risk factors**, just as they are for heart attacks. In contrast, elevated blood cholesterol has also been shown to protect against infections in the elderly, but this more apt to be a direct effect. Cholesterol is a key component of nerve cell membranes and synaptic communication connections. **Mental functions deteriorate when there is insufficient cholesterol, which is why the brain contains more than any other organ in the body. But if serum cholesterol is not available, where does cholesterol in the brain come from?**

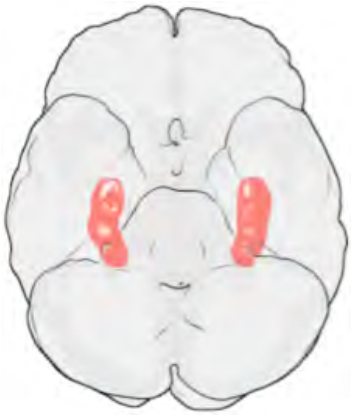
The answer to this was not revealed until less than ten years ago, when it was demonstrated that cholesterol is constantly churned out by glial cells that are found throughout brain tissue as well as in the spinal cord. They do not transmit electrical signals like neurons, but nourish and protect nerve cells by making myelin and maintaining homeostasis via repair activities and clearing waste products. Almost 90% of the brain is composed of glial cells and they are particularly abundant in the hippocampus, where there is some evidence that they can function as neurons in storing and retrieving memory. Research into this and allied areas confirms the belief that **Alzheimer's may be due to chronic low brain cholesterol**. All cells have a potential supply of amyloid in the form of amyloid precursor protein, and when there is not enough cholesterol due to increased demand or glial cell dysfunction, amyloid is made and substituted as a temporary replacement. This also explains why lipophilic statins that can pass through the blood brain barrier interfere with memory and cause amnesia by blocking glial production of cholesterol. A thorough discussion of this can be found in *Alzheimer's Solved* by Henry Lorin, which contains 77 pages of thousands of references that explain why and how low cholesterol can cause Alzheimer's.

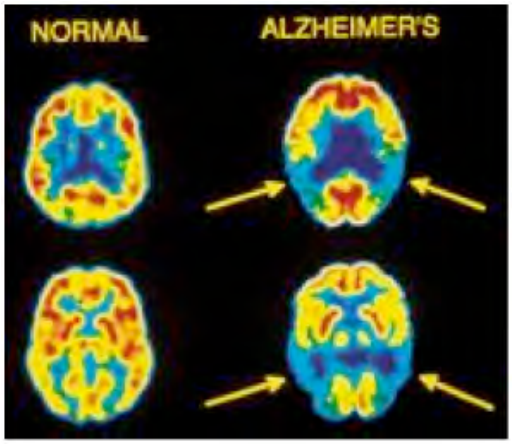
Stress And The Sinister Shrinking Of The Sea Monster – Are There Solutions?

Loss of memory for recent events occurs in most everyone as they get older. This is due to progressive age related reduction in the size and function of the hippocampus, which is involved in forming, storing and retrieving memories. However, the rate at which this happens and its severity varies considerably depending on genetic factors and other influences, especially stress. Stress results in increased secretion of cortisol, a hormone that also causes hippocampal atrophy. Patients suffering from depression, PTSD and other stress related disorders that produce chronic elevation of cortisol levels frequently complain of difficulty in remembering recent events. Stress also accelerates the aging process by reducing telomerase levels. But is there any evidence that increased stress or cortisol levels can cause Alzheimer's?

The answer appears to be yes based on a University of California study with a genetically modified mouse model of Alzheimer's. It found that when four-month-old animals were injected for just seven days with dexamethasone, which is similar to cortisol, beta-amyloid in the brain increased by 60 percent and formed plaques. Levels of tau protein that led to the formation of typical neurofibrillary tangles also increased, and the degree of both abnormalities was similar to that seen in untreated mice 8 to 9-months-old. Even more impressive were the results of dexamethasone in thirteen-month-old mice, which dramatically increased the formation of existing plaque and tangles. Salk researchers showed that increased stress also produced these two diagnostic changes in transgenic mice prone to develop Alzheimer's.

Elevated levels of cortisol have been reported in early stages of Alzheimer's and these mice studies suggest that stress could also hasten the onset or increase the severity of the disease in humans. To investigate this, 800 elderly Catholic nuns, priests, and brothers with no physical or mental health problems received a battery of 19 validated tests for memory and various cognitive functions and numerous others to measure depression, anxiety and stress susceptibility. These were repeated periodically over the next 5 years, during which 140 were diagnosed as having Alzheimer's. Subjects with the highest stress scores (top tenth percentile) were twice as likely to develop the typical signs and symptoms than those in the lowest tenth. **The high distress group was also 10 times more likely to experience a significant and progressive decline in memory, but had no significant difference in other cognitive functions.** And examination of the brain in the 54 with Alzheimer's who died, revealed that **less than 40% had sufficient amyloid plaque and tangles required to make this diagnosis**. While these confusing results failed to prove a clear link between stress and Alzheimer's, they did show that clinical diagnosis can have a poor correlation with the pathologic picture, and that while stress clearly impairs memory, it does not have the same deleterious effect on other cognitive functions seen in Alzheimer's. Nor does stress increase the neurofibrillary tangles and amyloid deposits thought to be responsible for mood and behavior changes, loss of concentration and other Alzheimer's stigmata.





What we do know is that stress causes a decrease in the size of the hippocampus and that this is also a consistent finding in Alzheimer's. As seen above to the left, humans have two hippocampi located in the temporal lobe on each side of the brain. In Alzheimer's, the hippocampus is the first structure affected and short-term memory starts to deteriorate. This is followed by an overall shrinkage of brain tissue as the disease progresses and the ventricles, chambers in the brain that contain cerebrospinal fluid, become significantly enlarged, as shown in the PET scan to the right.

Hippopotamus comes from the Greek *hippos* (horse) and *potamus* (river), and means horse of the river. Hippocampus was invented by a 16th century anatomist who thought a cross section of its slightly curved shape resembled a creature with a horse's forelegs and a dolphin's tail, hence *hippos* (horse) and *kampos,* (sea monster.) Since shrinkage of the hippocampus is the first objective sign of Alzheimer's, research has started to focus more on this component of the limbic system, which ties emotions to memories. A recent study showed that one of the earliest effects of stress is the formation of abnormal hippocampal tau. And while stress induced changes have always been attributed to cortisol, Salk researchers just reported that they are due to defects in corticotropin releasing factor receptors (CRFR1 & CRFR2) that mediate the body's response to stress, and that cortisol is not the culprit.

It seems surprising that despite tens of thousands of studies, there has been little improvement in the diagnosis and treatment of Alzheimer's since it was first described. Some reasons for this include: its varied and unpredictable course that make it difficult to evaluate any intervention; the possibility that it may have multiple and very different causes; assumptions that genetically altered animal studies apply to humans; research with opposing results as to the benefit and risks of estrogen, other hormones and a host of other substance; not recognizing that buzz words like "inflammation", "free radicals" and "antioxidants" that are loosely lumped together, can each consist of very different components; the likelihood that Alzheimer's is a multifactorial disease that requires APOE4 and other recently discovered genes, as well as external influences.

"Use it or lose it" still applies, and the best advice may be to keep mentally active by doing crossword puzzles and maintaining close contact with friends who can supply social support, a powerful stress buster. Nursing Home studies also confirm the benefits of stress reduction, both for patients and their caregivers, who are often more stressed. Novel stress reduction drugs that act on the hypothalamus and others that influence the expression of genes show promising prophylactic results — so stay tuned for more on this!

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Editor-in-Chief

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