Cognitive Impairment

How Stress Damages The Brain

A significant way to more effectively manage neurodegenerative disorders is the ability to effectively and conveniently monitor oxidative stress in the brain. It is well known that chronic stress shrinks certain regions of the brain. The hippocampus, a part of the limbic system or feeling brain located around the top of the brain stem, when under prolonged stress, suffers atrophy. This brain area is essential in learning by converting information from short-term into long-term memory and also for the checking of the new information with experience. (Alzheimer's?) With prolonged stress there is also an enlargement of the amygdala, a center for rage, aggression and fury, resulting in increased anxiety and aggression. With prolonged stress, the mind is blocked off from what it knows and cannot readily learn or master the present. When mentally blind, there is increased anxiety. Though Alzheimer's has more than one suspected contributing cause (heavy metals, toxins, exogenous estrogens, hyperhomocysteinemia, etc) how much is actually stressed induced is becoming a critical question. As the population continues to age, the number of people with Alzheimer's disease is expected to triple. About 5.4 million people are affected today about 1 out of every 8 Americans according to the **2011 Alzheimer's Disease Facts and Figures guide by the Alzheimer Association**, the prevalence doubles every five years after the age of 65.

The following articles should drive home how devastating stress is and hopefully begin to answer the question of which markers are effective in evaluating oxidative stress in the brain so that positive steps can be taken. Rather than hyping the brain with all types of brain food, the secret to top mental performance is to protect the brain from oxidative stress and keep it balanced. The brain already is constructed to function well. It should be a life habit to lessen stress (breathing, exercise, meditation, down time as rest, healthy diet, good life choices), to add in good lipids as in **Phosphatidylserine** (the brain is mostly lipid), to take the appropriate antioxidants (**BioProtect** (broad spectrum antioxidant), **Tocotrienols** (highly functional vitamin E), or **GSH Plus,** etc.) and include some **Acetyl-L-Carnitine** to cross the blood brain barrier facilitating metabolism. We may even notice some regain of brain function. It takes so little to protect so much.

"The Role of Oxidative Stress in Alzheimer Disease," Markesbery WR, Arch Neurol, December, 1999;56:1449-1452. Oxidative stress has been implicated in neurodegenerative diseases, including amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease and Alzheimer's disease. In Alzheimer's disease, there is an increased oxidation of brain lipids, carbohydrates, proteins and DNA. Some of the products of oxidation have been found in the major histopathologic alterations in Alzheimer's disease, which are neurofibrillary tangles and senile plaques. The oxidative modifications are associated with subtle inflammatory processes that are found in the Alzheimer's disease brain.

"Glucocorticoids, depression, mood disorders: structural remodeling in the brain." Bruce S. McEwen Metabolism: Volume 54, Issue 5, Supplement 1, May 2005, Pages 20-23. The hippocampal formation expresses high levels of adrenal steroid receptors and is a malleable brain structure that is important for certain types of learning and memory. It is also vulnerable to the effects of stress and trauma. The amygdala is an important target of stress and mediates physiological and behavioral responses associated with fear and strong emotions. The prefrontal cortex plays an important role in working memory and executive function and is also involved in extin1tion of learning. All three regions are targets of stress hormones, and stress is known to precipitate and exacerbate mood disorders. In long-term depressive illness, the hippocampus and prefrontal cortex undergo atrophy, whereas the amygdala is hyperactive in anxiety and mood disorders and may undergo a biphasic change in structure—increasing in size in acute depression and shrinking on long-term depression. In animal models of acute and chronic stress, neurons in the hippocampus and prefrontal cortex respond to repeated stress by showing atrophy that leads to memory impairment, whereas neurons in amygdala show a growth response that leads to increased anxiety and aggression. Yet, these are not necessarily "damaged" and may be treatable with the right medications. The mechanisms that distinguish between protection and damage of brain cells from stress are discussed.

"Evidence of increased oxidative damage in subjects with mild cognitive impairment." J. N. Keller, PhD, et al. Neurology 2005;64:1152-1156 .**The objective was to** determine if increased levels of oxidative damage are present in the brains of persons with mild cognitive impairment (MCI), a condition that often precedes Alzheimer disease (AD). The authors assessed the amount of protein carbonyls, thiobarbituric acid-reactive substances (TBARS), and malondialdehyde in the superior and middle temporal gyri (SMTG) and cerebellum of short postmor-

tem interval and longitudinally evaluated normal subjects and those with MCI and early AD. Results: Elevated levels of protein carbonyls (~25%), malondialdehyde (~60%), and TBARS (~210%) were observed in the SMTG of individuals with MCI and early AD vs normal control subjects. The elevation in TBARS was associated with the numbers of neuritic but not diffuse plaques. Levels of protein carbonyls increased as delayed verbal memory performance declined. Conclusion: Oxidative damage occurs in the brain of subjects with mild cognitive impairment, suggesting that oxidative damage may be one of the earliest events in the onset and progression of Alzheimer disease.

"Cognitive Impairment and Mortality in a Cohort of Elderly People," Gale CR, Martyn CN, Cooper C, BMJ, March 9, 1996;312:608-611. In a 20-year follow up study of randomly selected elderly subjects from 8 areas in Britain, 921 men and women were evaluated for cognitive function between 1973 and 1974. Cognitive impairment was associated with increased mortality, especially from ischemic stroke. Cognitive function was poorest in those with the lowest vitamin C status, whether measured by dietary intake or plasma ascorbic acid concentration. The relationship between vitamin C status and cognitive function was independent of other variables. Vitamin C status may be a determinant of cognitive function in the elderly due to its effect on atherogenesis. A high vitamin C intake may be protective against cognitive impairment and cerebrovascular disease.

"Cohort Study of Vitamin C Intake and Cognitive Impairment," Paleologos M, et al, Am J Epidemiol, 1998;148(1):45-50. In a 4-year follow-up study involving 117 adults from a retirement community, vitamin C supplementation was associated with a lower prevalence of more severe cognitive impairment. Vitamin C may protect against cognitive impairment.

"Ascorbate: An Antioxidant Neuroprotectant and Extracellular Neuromodulator," Rebec, George V., Metals and Oxidative Damage in Neurological Disorders, 1997;Chapter 9:149- 173. Vitamin C is important in the synthesis of collagen, the promotion of iron absorption, the regulation of cholesterol synthesis and elimination, and for a variety of normal bodily functions. The brain has the highest rate of oxidative activity of any organ. Vitamin C can influence brain function in ways beyond its role as an antioxidant. Vitamin C can interact with neural tissue, suggesting a direct effect on neural function, including changes in electrical impulse flow, transmitter release, and receptor binding. Most mammals rely on enzymes in the liver to synthesize ascorbate from glucose, while others such as primates and guinea pigs must obtain it through the diet as water-soluble vitamin C. Increases in brain ascorbate can be detected within minutes after systemic injection of 1,000-2,000 mg/kg in rats and mice. The high level of vitamin C that is maintained in brain tissue, and the large number of stimuli that trigger its release into extracellular fluid from neural and, possibly, glial sources, underscores the importance of this vitamin for normal brain function. Vitamin C provides some protection against oxidative stress associated with the normal operation of dopaminergic and glutamatergic neurons. Vitamin C has been shown to influence dopamine-mediated behavioral effects and to potentiate the synaptic action of both dopamine and glutamate on neostriatal neurons. Vitamin C appears to function as an extracellular modulator of synaptic transmission.

Long-Term Effects of Stress Reduction on Mortality in Persons ≥55 Years of Age with Systemic Hypertension. Bogash J, Research Updates 5-16-2005,www.lifecarechiro.com. So stress reduction makes you healthier and lowers your risk of dying from many diseases. But a 49% decrease in risk of cancer in participants performing meditation? That is cutting your risk of cancer in half from meditation alone. There was also a 23% reduction in all cause mortality and 30% reduction in cardiovascular mortality. These numbers are staggering.

"Vitamin E and Other Antioxidants in Neuroprotection," Behl C, Int J Vitam Nutr Res, 1999;69(3): 213-219. Lipophilic free radical scavengers such as vitamin E and estrogen protect nerve cells against oxidative stress-induced cell damage and ultimately cell death. The concept of antioxidants as neuroprotectants has a promising future, especially with such conditions as Alzheimer's disease, which has a variety of hypothesized pathophysiologies which include a neurotransmitter deficiency/acetylcholine hypothesis, energy metabolism hypothesis, arthritis of the brain hypothesis, amyloid cascade hypothesis and oxidative stress hypothesis. (Consider E High Gamma -200, E-Mulsion 200 or Tocotrienols.)

"Tocotrienols: Constitutional Effects in Aging and Disease." Sebastian Schaffer[2], Walter E. Müller and Gunter P. Eckert: J. Nutr. 135:151-154, February 2005. Tocotrienols are Vit E's more powerful cousin and usually kept in the closet. However, they are present in some of the higher quality vitamins as well as a wide variety of foods like rice bran and certain oils like palm. We have known that they have some powerful antioxidant properties for awhile, but this review suggest additional benefits of lowering cholesterol and, as a wonderful bonus considering the increase in neurodegenerative disorders, reducing glutamate-induce neurotoxicity. This would suggest that those people with seizures or at increased risk of Alzheimer's or Parkinson's should put this one on the protective list. (Consider Tocotrienols)

"Glutathione, Oxidative Stress and Neurodegeneration," Schulz JB, Lindenau J, Seyfried J, Dichgans J, Eur J Biochem, 2000;267:4904- 4911. Glutathione is an important intracellular antioxidant. It plays a role in protecting the cell against a variety of oxidants. In Parkinson's disease, a reduction in total glutathione concentrations in the sub-

stantia nigra has been associated with preclinical stages of the illness. Glutathione does not cross the blood-brain barrier. Altered antioxidant defenses support the concept that oxidative stress plays a role in the pathophysiology of Parkinson's disease. Glutathione transferases are a group of detoxification enzymes involved in the metabolism of pesticides and other toxins. Glutathione transferases have antioxidant activity and are involved in the metabolism of dopamine. Parkinson's disease patients have a defect in oxidative phosphorylation. An increase in brain glutathione levels should result in clinical benefit and/or neuroprotection in animal models and in human disease. (GSH Plus contains glutathione and its main replenishers, N-Acetyl-L-Cysteine and glycine, which do cross membranes easily.)

"Neurodegenerative Disorders in Humans: The Role of Glutathione in Oxidative Stress-Mediated Neuronal Death," Bains JS, Shaw CA, Brain Res Rev, 1997;25:335-338. In this review, oxidative stress-mediated neuronal loss may be initiated by a decline in the antioxidant molecule glutathione. Glutathione in the nervous system acts as a free radical scavenger, redox modulator of ionotropic receptor activity and possibly a neurotransmitter. Glutathione depletion can enhance oxidative stress and may increase levels of excitotoxic molecules, which may initiate cell death in specific neuronal populations. Evidence for a role of oxidative stress and reduced glutathione status is found in Lou Gehrig's disease, Parkinson's disease and Alzheimer's disease.

"Meta-Analysis of Double Blind Randomized Controlled Clinical Trials of Acetyl-L-Carnitine Versus Placebo in the Treatment of Mild Cognitive Impairment and Mild Alzheimer's Disease," Montgomery SA, Thal LJ, Amrein R, Int Clin Psychopharmacol, 2003;18:61-71. In a meta-analysis of double-blind, placebo-controlled trials of at least 3 months' duration, with daily doses of acetyl-L-carnitine at 1.5 - 3.0 g/day, there was a significant advantage for acetyl-L-carnitine compared with placebo for integrated summary effects and the Clinical Global Impression of Change. There was benefit seen on both clinical and psychometric tests. The benefit of acetyl-L-carnitine was first seen at the first assessment at three months and then increased with time. Acetyl-L-carnitine was well tolerated in the studies. (Carnitine as Acetyl-L-Carnitine very effectively crosses the blood brain barrier.)

"Action of Acetyl-L-Carnitine in Neurodegeneration and Alzheimer's Disease," Calvani M, Carta A, et al, Ann N Y Acad Sci, 1992;663:483-486. Acetyl-L-carnitine can be freely exchanged across membranes and can provide acetyl groups for the regeneration of acetyl-CoA. Acetyl-L-carnitine is able to reverse hippocampal and prefrontal neuronal loss and lipofuscin accumulation in aging animals, as well as improve learning and memory performances in these animals. Acetyl-L-carnitine helps prevent lipid peroxidation in aged cells and increases levels of reduced glutathione and ubiquinol, which are antioxidants. Acetyl- l-carnitine sustains electron transport, enhances oxidative phosphorylation, reverses the impairment of DNA/RNA transcriptase, and restores age-induced impaired turnover of mitochondrial inner membrane proteins. Acetyl-L-carnitine should be considered a neuroprotective agent, especially in dementia, due to its antioxidant action, its ability to stabilize cell membrane function, and its ability to enhance cholinergic transmission.

Homocysteine, Folate, and Vitamin B-12 in Mild Cognitive Impairment, Alzheimer's Disease, and Vascular Dementia," Quadri P, Fragiacomo C, et al, Am J Clin Nutr, 2004;80:114-122. Plasma total homocysteine, serum folate and serum vitamin B12 levels were evaluated in 55 non-demented elderly control subjects, 81 mildly cognitively impaired subjects, and 92 demented patients who were mainly in a mild disease stage with a clinical diagnosis of Alzheimer's disease in 74 subjects and vascular dementia in 18 (mean age range 75.6 to 80.5 years, 34-40% male). Subjects in the lowest third of folate levels had higher odds ratios for mild cognitive impairment at 3.1 and dementia at 3.8. Hyperhomocysteinemia was significantly associated with dementia, with an odds ratio of 4.3, and Alzheimer's disease, with an odds ratio of 3.7. In individuals with a Clinical Dementia Rating of 0.5, the mean Mini-Mental State Examination score was significantly lower in the highest homocysteine tertile compared with the lowest tertile. These data suggest that relative folate deficiency may precede Alzheimer's disease and vascular dementia onset. Hyperhomocysteinemia may also be an early risk factor for cognitive decline in the elderly, but its role in dementia development needs further evaluation. (Consider B12 2000 Lozenges.)

"Physical Activity and Risk of Cognitive Impairment and Dementia in Elderly Persons," Laurin D, Verreault R, Lindsay J, et al, Arch Neurol, March 2001;58:498-504. In studying 9,008 randomly selected men and women who were 65 years of age or older, 4,615 completed a 5-year follow-up. Of these, 3,894 were without cognitive impairment, 436 were diagnosed as having cognitive impairment-no dementia, and 285 were diagnosed as having dementia. Compared with no exercise, physical activity was associated with lower risks of cognitive impairment, Alzheimer's disease and dementia of any type. There was a trend toward increased protection with greater physical activity. High levels of physical activity reduced the risk of cognitive impairment, Alzheimer's disease and dementia of any type. (Pearl: The problem with traditional drug-based medicine and also nutritional supplementation is that people so often look for "the magic bullet," instead of doing things that are basic to health which have greater significance and cost effectiveness such as physical activity. Physical activity reduces dementia and cognitive impairment in the elderly. Getting our population more active, and expecting activity until the end of our lives, is something that is so vitally important to sustain a health care system that it can never be over-emphasized. To the elderly patients it

should be "move, move and move more," whether it be simple walking, Tai Chi, yoga, stretching, dance, weight lifting or anything that puts the body into motion. People should expect this to be part of their lives until the day they die. This would greatly enhance their functionality until their death.)

"Estrogen Plus Progestin and the Incidence of Dementia and Mild Cognitive Impairment in Postmenopausal Women: The Women's Health Initiative Memory Study: A Randomized Controlled Trial," Shumaker SA, Legault C, Rapp SR, et al, JAMA, May 28, 2003;289(20):2651-2662. In a study of 4,894 females who were 65 years of age or older and had participated in the Women's Health Initiative Study, 4,532 (92.6%) were postmenopausal and free from dementia at the time of this trial. Individuals received either 1 tablet daily of 0.625 mg of conjugated equine estrogen plus 2.5 mg medroxyprogesterone acetate (n=2,229), or a matched placebo (n=2,303). The mean follow-up time to evaluation was 4.05 years. Sixty-one women were diagnosed with probable dementia, of whom 66% were in the estrogen plus progestin group compared with 34% in the placebo group. The hazard ratio for probable dementia was 2.05 in the estrogen plus progestin group. This increased risk would result in 23 additional cases of dementia per 10,000 woman per year. Alzheimer's disease was the most common type of dementia in both study groups. Use of hormone therapy to prevent dementia or cognitive decline in women who are 65 years of age or older is not recommended. (Ca-D-Glucarate helps clear excess natural hormones, etc.)

"Silica and Aluminum in Drinking Water and Cognitive Impairment in the Elderly," Jacqmin-Gadda, Helene, et al, Epidemiology, May, 1996;7(3):281-285. In 3,777 French subjects 65 years of age or older there was an inverse relationship between calcium levels in drinking water and cognitive impairment. High levels of aluminum in the water had an adverse effect when silica concentrations were low but a protective effect when the pH and the silica levels were high. Aluminum concentrations in drinking water may be associated with a high risk of cognitive impairment only when the concentration of silica is low. (Consider Basic Nine (trace minerals) which contains 100 mcg organic silica/tablet and also Ca/Mg-Zyme.)

Further notes: Bio-Mega 3 is a DHA source and also effective as a natural anti-inflammatory. Nuclezyme Forte supplies the normal B vitamins, vitamin A, etc, and as it was designed specifically for mind and memory, it has DNA, RNA, zinc, and PABA. It has a good history of holding up clinically. We also need to exercise the mind as well as the body, as memory loss is related to aging. If we don't use it, we will lose it. Those that continue to study, read and use the mind will score better on IQ tests as they age.