

BASIC SCIENCE ASPECTS OF THE MITOCHONDRIA SECTION XI

CELLULAR AND MITOCHONDRIAL PERTURBED ENERGY METABOLISM AND NEURONAL DEGENERATION IN ALZHEIMER'S AND PARKINSON'S DISEASES

Synaptic degeneration and death of nerve cells are seen in both Alzheimer's disease and Parkinson's disease, the two most prevalent age-related neurodegenerative disorders. In Alzheimer's Disease, neurons in the hippocampus and basal forebrain which subserve learning and memory are invoked. In Parkinson's Disease, dopamine-producing neurons in the substantia nigra striatum which control body movements degenerate. Studies of postmortem brain tissue from both Alzheimer's and Parkinson's Disease patients show increased oxidative stress, mitochondrial dysfunction and impaired glucose uptake in involved neurons.

Recently, Mark A. Smith and co-workers at the Institute of Pathology in Case Western Reserve University in their review on Oxidative Stress and Alzheimer's disease (*Biochemica et Biophysica Acta* 1502 (2000) 139-144) noted:

“For Alzheimer's disease (AD), the majority of research resources have been dedicated to studies on the pathogenesis of the intraneuronal filamentous inclusions, known as neurofibrillary tangles (NFT), and the extracellular senile plaques. This focus has often been detrimental to the advancement of other theories. Consequently, there is a large void in our understanding of the

pathogenesis of AD, namely the underlying mechanism of the disease. Nonetheless, in recent years, research has clearly pointed to the importance of oxidative imbalance in AD.”

Parkinson’s Disease is better understood due to the availability of animal models and the ability to create a model of Parkinson’s Disease with some toxins. This has recently been described in great detail by Sanberg, P, Nishino, HH, Borlongan CV (Eds), in “Mitochondrial Inhibitors and Neurodegenerative Disorders”, Humana Press, Totowa, NJ (2000).

Recent data has shown that both diseases manifest profound alterations in energy metabolism, increased insulin resistance, and dysregulation of glucose metabolism. Current research shows that dietary restrictions can forestall the development of both diseases. This tends to show a metabolic component for these diseases, as well as offering the possibility of prevention for both of these diseases. Evidence consisting of brain imaging studies documents reduced glucose uptake in brain cells of living Alzheimer’s sufferers. Cellular studies show reduced mitochondrial function in affected brain regions, as well as fibroblasts, in both Alzheimer’s and Parkinson’s Disease patients. Any consideration of the pathogenesis of Parkinson’s and Alzheimer’s Disease has to include the fact that, in both, increasing age is a major risk factor and increased

oxidative stress, mitochondrial dysfunction and metabolic abnormalities are prominent features of aging in all body systems, including the brain.

In Alzheimer's Disease, the hippocampal, entorhinal cortex, basal forebrain, and neocortical association areas degenerate whereas, in Parkinson's Disease, there is degeneration of dopaminergic neurons in the substantia nigra.

Currently, the fashion in research is an attempt to find genetic explanations for all diseases and genetic theories of the causation of Alzheimer's and Parkinson's Disease abounds in all the current literature. This is frequently to the exclusion of consideration of older, well-established data concerning both nutritional deficiencies and accumulated toxicities from both heavy metals and organophosphate pesticides.

To the extent that genetic factors may come into play in selective vulnerability brain areas as well as in populations, these genetic studies should, of course, be pursued, but not to the extent of losing sight of nutritional and environmental factors, which have been shown for years to influence both of these diseases.

The first and most obvious nutritional deficiency involved in the pathogenesis of dementia is B vitamin deficiency in general, and thiamine deficiency in particular. Thiamine is a necessary co-enzyme for several steps for ATP production and mitochondria.

A decade ago, Butterworth and Besnard, University of Montreal reported that brains of Alzheimer's Disease patients showed significant decreases in pyruvate dehydrogenase, alphaketoglutarase, and transketerase. (*Metabolic Brain Diseases* (1990) 5(4):179-84, "Thiamine Dependent Enzyme Changes in the Temporal Cortex of Patients with Alzheimer's Disease")

It has been reported that Alzheimer's patients had significantly lowered thiamine levels. (Gold, et al, *Archives of Neurology*, (1995) "Plasma and Red Blood Cell Deficiency in patients with Dementia of the Alzheimer's Type") and Kish, *Annals of the NY Academy of Science*, (1997) 826:218-28, "Brain Energy Metabolising Enzymes in Alzheimer's Disease, Alpha ketoglutarate dehydrogenase complex and Cytochrome Oxidase")

In 1997, Calingasan and co-workers at Cornell Medical College" reported that Thiamine deficiency alters amyloid precursor protein metabolism and is involved in the pathogenesis of Alzheimer's Disease. (*Neuroreport* 8(11):2631-4, "Thiamine deficiency alters APP but not presenilin-1 immunoreactivity in vulnerable brain regions")

In 1988, Gibson and Co-workers, Department of Neurology, Cornell University Medical College, reported that in Thiamine deficient Alzheimer's patients, activities of the alpha-ketoglutarate dehydrogenase complex were reduced more than 75 % and transketolase was reduced more than 45%. They

concluded that activities of thiamine dependent enzymes in brains are involved in the pathogenesis of Alzheimer's disease. (*Archives of Neurology*, 45(8):836-40, "Reduced Activities of Thiamine-dependent enzymes in the brains and peripheral tissues of patients with Alzheimer's disease")

This sampling of literature should suffice to demonstrate the pivotal role of thiamine deficiency in the pathogenesis of brain neurodegenerative disorders.

What has not been appreciated is the number of factors which can produce relative thiamine deficiency, particularly in the elderly. Some of these are alcohol ingestion in which the alcohol dehydrogenase in the liver manditorily uses thiamine as a co-enzyme and will deplete thiamine from all tissues for this purpose. Another is the presence of thiaminase in several foods, most notably in raw fish. Up until 10 years ago, the presence of large amounts of heat-labile thiaminase in raw fish was a matter of importance, largely in animal feeding. Presently, however, there has been a large increase in the consumption of raw fish by human beings in the form of sushi. There are now sushi bars in most towns and cities and a large number of Americans consume sushi usually, together with alcoholic beverages, without any consideration of the fact that raw fish and alcohol consumption can almost completely deplete thiamine in human beings. High carbohydrate diets increase the need for thiamine. In the elderly, particularly those living alone, there is an increased reliance on tea and toast to the virtual

exclusion of other foods. Thiamine absorption is frequently impaired in the elderly due to intestinal problems and diarrhea. Alpha ketoglutarate dehydrogenase complex is an essential step in the Krebs Cycle and is solely dependent on thiamine as a co-enzyme. Thiamine deficiency produces a severe disruption in electron transport and ATP production and, eventually, leads to apoptosis of neurons which is a hallmark of both Alzheimer's Disease and Parkinson's Disease.

Alzheimer's disease is a nutritional deficiency disease. It is at the end of the spectrum of thiamine deficiency diseases, including Beriberi and Wernicke-Korsakoff Syndrome. It is the chronic, subclinical manifestation of protracted thiamine deficiency, superimposed on chronic aluminum and other metal toxicity, all of which, ultimately, combine to produce loss of mitochondrial function and cell death in cholinergic neurons.

Thiamine supplementation cannot restore neurons lost in this fashion but can restore adequate energy production in remaining brain cells and can do much to prevent these diseases. Thiamine deficiency is commonly seen in people who are also victims of environmental toxins, particularly aluminum toxicity, and particularly the toxicity of aluminum fluoride, which is commonly seen in municipal water supplies. These water supplies are treated with aluminum and fluoride, which combine to produce aluminum fluoride. People who consume

water from such municipal water supplies accumulate aluminum fluoride, which is poorly excreted. People who consume foods prepared in aluminum cookware and who consume aluminum containing antacids are also at high risk. Individuals who have both thiamine deficiency and high levels of aluminum fluoride are at high risk for development of neurodegenerative diseases. To this must be added the effects of pesticides, such as organophosphates which inhibit Complex I and IV of the electron transport chain. People with dental restorations containing mercury are also at high risk.

The first insult is aluminum toxicity which, frequently, begins in the first days of life because most infant formulas contain aluminum. (McGraw, M.D., Bishop, N.; and Jameson, R., et al. "Aluminum content of milk formulae and intravenous fluids used in infants." *Lancet* 1:157, 1986); (Bishop, N.; McGraw, M, and Ward N. "Aluminum in infant formulas." *Lancet*. March 4, 1989); (Freundlich, M.; Zillervelo, G.; Abitbol, C; Strauss, J.; Faugere, M.C.; and Malluche, H.H. "Infant formula as a cause of aluminum toxicity in neonatal uraemia." *Lancet* ii:527-5299, 1985); and (American Committee on Nutrition. "Aluminum toxicity in infants and children: *Pediatrics* 78:1150-1154, 1986).

From this beginning, exposure to aluminum ingestion is fairly consistent and unrelenting throughout life. A hypothetical individual born in 1940, after his or her initial exposure in infant formulas was exposed to aluminum in the drinking

water, oftentimes in the form of aluminum fluoride complexes. His or her food was very likely to have been cooked in aluminum pots and pans. When this produced gastric upset, the relief was by consumption of antacid which contained as their main ingredient, aluminum hydroxide. The first visit to the dentist compounded the problem by the addition of mercury in the form of amalgam dental restorations, and lead was added from the daily water piped into the home through lead pipes. After 1960, the introduction of aluminum foil added to the contamination of most foodstuffs.

By 1970, when our hypothetical individual was 30 years of age, 18 million kilograms (39.6 million pounds) of sodium aluminum phosphate was used in the American food supply. That same year 3.6 million kilograms of sodium aluminum sulfate, 510,000 kilograms of aluminum sulfate, 230,000 kilograms of aluminum ammonium sulfate, and 3,800 kilograms of aluminum potassium sulfate were added to the American food supply as direct additives. (Weiner, M.A., "Reducing the Risk of Alzheimer's", New York, Stein and Day, 1987, pp. 63).

The manufacture of aluminum produces a toxic by-product, fluoride, which is sold to municipalities to be added to the municipal water supply, allegedly to prevent dental decay. As noted above, this is added to water supplies which have been processed with aluminum compounds. The result is an aluminum-fluoride compound, so that if our hypothetical individual only ate bread and drank water,

his or her exposure to aluminum ingestion was extremely high. (Shore D, Stuart M, Sprague G, Mayor GH, Moreno C, Apostoles PS and Wyatt RJ, Sept./Oct. 1985. "Aluminum-Fluoride Complexes: Preclinical Studies". *J. Envir., Path., Tox., & Onc.*, 6:9), (Spencer H, Kramer L, Norris C, Osis D, and Wiatroski E., 1980a. "Effect of aluminum on fluoride and calcium metabolism in man". In: *Trace Substances in Environmental Health XIV*; Hemphill DD (Ed.) Univ. of Missouri, Columbia), Spencer H, Kramer L., Norris C., and Wiatroski E. 1980b. "Effect of aluminum hydroxide on fluoride metabolism". *Clinical Pharmacology and Therapeutics*, 28(4):529-35)

Aluminum and all of its compounds are extremely neurotoxic. It is concentrated in neurons, where it interferes with the balanced production of proteins and enzymes in brain cells.

When B vitamin and, particularly, thiamine deficiency is added to this situation, metabolic disorder is set in motion in the form of progressive neurodegeneration, particularly of cholinergic neurons, those involved in Alzheimer's disease.

Depending on variables, our hypothetical individual born in 1940 and living in the 20th Century, would begin to exhibit the early signs of Alzheimer's Disease at somewhere between 55 and 65 years of age. Some of the variables concern whether or not the individual consumed significant amounts of antacid tablets or

liquids, whether or not the individual developed heart failure for which he or she was treated with diuretics which deplete thiamine; whether or not the individual takes Digoxin which further depletes thiamine; whether they drink alcoholic beverages, or eat raw fish, or other foods which contain thiaminase. In summary, development of Alzheimer's Disease depends on how much aluminum he or she ingested and how little or how much thiamine was available to serve as essential co-enzymes in the Krebs cycle.

An individual born in 1940, probably has had far less exposure than his or her children are now experiencing. In the future, it is to be expected that Alzheimer's Disease will make its appearance at an earlier age and more individuals will be affected than individuals born before 1960.

Currently, most research in the pathophysiology of Alzheimer's Disease is concentrated in genetics which, to date, has produced no useful information and is not likely to do so in the future, since Alzheimer's is simply not a genetic disease or disorder but simply a nutritional disorder compounded by aluminum and other metal toxicants.

The thiamine deficiency contribution to Alzheimer's etiology is well documented and it is highly likely that the other B vitamins contribute as well.

Metal toxicity includes many more metals than aluminum; mercury, lead, cadmium, zinc, copper and iron are also involved.

Genes are involved, since toxic metals, particularly aluminum, in neurons, concentrate in the nucleus where they interfere with the proper function of genes and the production of RNA.

It should be remembered that 80% of the mitochondrial respiratory function is controlled from the nucleus DNA where proteins and enzymes are encoded. Most of the proteins and enzymes used in mitochondrial function are produced in cytoplasmic ribosomes and imported into the mitochondria; these pre-proteins must be transported through the contact points of the mitochondria where chaperones aid in the unfolding and folding of these proteins. Amyloid deposits are essentially proteins misfolded and unable to be imported into the mitochondria. They remain outside the mitochondria to produce neurofibrillary tangles and amyloid bodies. They are a by-product of the effects of toxins on that portion of the nucleus which encodes proteins for the mitochondria. Their presence is indicative of the presence of Alzheimer's Disease. The amyloid bodies and tangles interfere with energy production through a deficiency of thiamine and other B complex vitamins which are essential co-enzymes in the Krebs cycle and electron transfer chain. (Serpell, LC; Sunde, M; Benson, MD; Tennet, GA, Pepys, MB, Fraser PE, "The Protofilament Substructure of Amyloid Fibrils", *J. Mol. Biol.* (2000) 300:1033-1039), (Parker, WD Jr., Haas R, Stumpf DA, Parks, J, Eguren LA and Jackson C., "Brain mitochondrial metabolism in experimental thiamine

deficiency”, *Neurology* 34 (11): 1477-1481); (Parker WD Jr., Parks J, Filley CM, and Kleinschmidt-DeMasters BK, “Electron transport chain defects in Alzheimer’s disease brain”, *Neurology* 44(6):1090-1096); (Todd, KG and Butterworth RF, “Mechanisms of Selective Neuronal Cell Death due to Thiamine Deficiency” in “Oxidative/Energy Metabolism in Neurodegenerative Disorders”, Bass JP, McDowell, FH (Eds), *Annals of the New York Academy of Sciences*, Vol 893 (1999)); (Mantyh PW, Ghilardi JR, Rogers S, DeMaster E, Allen CJ, Stimson ER, and Maggio JE, “Aluminum, iron, and zinc ions promote aggregation of physiological concentrations of beta-amyloid peptide”, *J. Neurochemistry*, 61(3):1171-1174 (1993));

In the elderly, an additional risk factor is polypharmacy. Many pharmaceuticals directly affect thiamine. The administration of antibiotics, in particular, increases thiamine requirements. Since pharmaceuticals are seldom monitored for their effect on thiamine levels, the effect of many pharmaceuticals on this is completely unknown. Many Americans over 60 consume 12 to 15 pharmaceuticals daily. When this is added to inadequate thiamine intake, increased thiamine requirement and years of accumulation of neurotoxins, the question becomes not, *will* they suffer neurodegeneration but, *when they will* suffer neurodegeneration. The next question is whether their neurodegeneration

will first manifest itself as Alzheimer's Disease or Parkinson's Disease and, for many unfortunates, perhaps both.

Post-menopausal women with estrogen deficiency are particularly vulnerable to Alzheimer's Disease. It is well-established that high caffeine intake and nicotine intake bear an inverse relationship to the incidence of Parkinson's and Alzheimer's Disease. The incidence of neurodegeneration in people who drink a lot of coffee and smoke cigarettes is considerably smaller than those people who, for reasons of health concerns, avoid caffeine and nicotine, both of which are mitochondrial stimulants. Oddly, the administration of nicotine by skin patch is not nearly as effective as cigarette smoking in preventing neurodegenerative diseases.

It should be emphasized that the thiamine deficiency referred to here, is a relative thiamine deficiency, which is far less than that required to produce frank Beriberi or Wernicke-Korsakoff Syndrome. The effect of this is slow and cumulative, as are the effects of slowly accumulated neurotoxins.

It is highly likely that both Alzheimer's Disease and Parkinson's Disease occurred rarely before the 20th Century. Prior to the 20th Century, most people did not over-eat. Since caloric restriction prevents or long-delays the appearance of these neurodegenerative diseases, much of the blame for the appearance of these

diseases in the 20th Century may be the result of over-consumption under-nutrition, which was seldom seen prior to the 20th Century.

It is highly likely that the processes leading to the development of Parkinson's and Alzheimer's Disease are present and, to some degree, operative in all Americans and Central Europeans. For this reason, a concerted effort should be made to halt these processes before they result in frank dementia, movement disorders, or both. To this end, everyone should avoid the use of foods and drinks to which aluminum have been added. This includes baked goods which use aluminum-based rising agents; over-the-counter and prescription drugs containing aluminum; intravenous fluids containing aluminum and all liquids containing water from municipal water supplies. In addition, the ingestion of B vitamins, in much larger quantities than current recommended daily allowances should be regularly consumed. This entails the entire B vitamin complex. Ginkgo Bilobia extracts are also helpful. (Zhu L Wu J Liao H Gao J Zhao XN Zhang ZX "Antagonistic effects of extract from leaves of Ginkgo biloba on glutamate neurotoxicity". *Acta Pharmacol Sin* 1997 JUL;18(4):344) Klein J Chatterjee SS Loffelholz K, "Phospholipid breakdown and choline release under hypoxic conditions: Inhibition by bilobalide, a constituent of Ginkgo biloba", *Brain Res* 1997 MAY 2;755(2):347-350), (Kanowski S Herrmann WM Stephan K Wierich W Horr R, "Proof of efficacy of the Ginkgo biloba special extract EGb 761 in

outpatients suffering from mild to moderate primary degenerative dementia of the Alzheimer type or multi- infarct dementia (Reprinted from *Pharmacopsychiat*, vol 29, pg 47-56, 1996).” *Phytotherapy* 1997 MAR;4(1):3-13), (Nathan, P., “Can the cognitive enhancing effects of Ginkgo biloba be explained by its pharmacology”, *Medical Hypotheses* (2000) Dec; 55(6):491-493)

Persons over 50 should seriously consider undergoing a course of EDTA Chelation and a serious, prolonged, detoxification process such as that entailed in the use of Badmaev 269 and Ecomer. They should regularly consume supplements containing N-acetyl cysteine, N-acetyl inositol, choline, and daily supplementation of all essential enzymes, including Pancreatin, Pepsin, Rutin, Bromelain, Trypsin, Papain, Soy Isoflavones, Chymotrypsin, Shitake Mushroom Powder, *Dionaea Muscipula* Extract (Venus Fly Trap).

Real cheese is, however, an excellent source of nutrition. However, processed cheese food contains large amounts of aluminum to enhance its melting point. Therefore, commercially prepared cheeseburgers must be strictly avoided. A diet high in fibers and relatively low in calories should be maintained. Persons should avoid excessive alcohol intake, and should practice eating foods rich in B vitamins while consuming alcohol. The intake of alcohol should be limited to 2 ounces per day, if alcohol is to be consumed at all. This regimen cannot restore nerve cells that have been destroyed, but brain cells can be and are replaced at a

slow rate by natural bodily processes. This can only occur if the remaining neurons are kept in a state of optimal mitochondrial function and energy production.

Excellent dietary advice with specimen menu's for avoidance of Alzheimer's and Parkinson's Disease are contained in Casdorff and Walker, "Toxic Metal Syndrome", Garden City Park, New York, Avery Publishing Company, (1995).

The pivotal role of mitochondrial function in the pathogenesis of neurodegeneration has only recently come to be recognized by researchers and is virtually never considered by clinicians.

The emphasis here on thiamine deficiency should not serve to diminish the importance of other B vitamins, deficiencies of which commonly occur together with thiamine deficiency. It is highly likely that all B complex vitamins play a pivotal role in maintaining adequate mitochondrial function. Deficiencies in niacin, vitamin B 12, are well known to produce dementia. An example is Pellagra, (B3 deficiency) which, in its classic form, is characterized by dementia and diarrhea, as well as skin diseases.

Attempts to prevent and reverse these dementia's likely should include adequate intake of all B vitamins, elimination of neurotoxic substances, the

elimination of accumulated stores of these toxic substances in the body, and the absolute avoidance of water from municipal water supplies.

A supplement protocol based on the following recommendations: 1) High Potency Multiple Vitamins containing the entire B vitamin complex in amounts greater than the RDA, 2) Vitamin C 500 – 1,000 mg three times daily, 3) Vitamin E 400-800 I.U. daily, 4) Fish Oil containing Omega 3 and Omega 6 Fatty Acids, 5) Thiamine 3-8 mg daily, 6) Phosphatidylserine 100 mg 3 times daily, 6) Phosphatidylcholine 100 mg 3 times daily, Phosphatidylinositol 100mg 3 times daily, 7) Ginkgo Biloba Extract (24% ginkgo flavoglycosides), 80 mg three times daily, 8) Badmaev, 1-2 tablets three times daily with meals, 9) Ecomer one to two capsules two to three times daily, 10) Coenzyme Q10 100-200 mg per day, 11) Regular hair mineral analysis to rule out aluminum or other heavy metals, 12) EDTA Chelation where indicated by hair mineral analysis, 13) A diet containing generous servings of deep sea fish from Northern waters, 14) Never, under any circumstances, consume water from municipal water supplies, including coffee, tea and other beverages prepared from such water supplies, 15) Methylcobalamin (active B12), 1,000 micrograms twice daily and, 16) antioxidants.

This basic regimen must, of course, be modified to suit the individual needs and conditions of the patient to be treated. It is a guideline, not an inflexible standard.

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