Alzheimer's Disease and Other Autoimmune Degenerative Conditions: the Mercury Connection

Bernard Windham (Ed.)

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B. Windham (Editor)

1.1 Introduction and mercury exposure

There has been a huge increase in the incidence of degenerative neurological conditions in virtually all Western countries over the last 2 decades (574, 580, 594). Alzheimer's disease is the leading cause of dementia in the elderly. The increase in Alzheimer's and other dementia has been over 300%. The primary cause appears to be brain inflammation related to increased exposures to toxic pollutants and bad dietary habits, as well as oxidative stress and depletion of neurotransmitters such as acetylcholine (445, 574, 577, 580, 594, 598, 158, etc.). These appear to be factors in formation of advanced glycation end products (AGEs) and senile plaques of beta-amyloid peptides, hyperphosphorylation of Tau, and neurofibrillary tangles-as seen in Alzheimer's patients.

Mercury is known to be one of the most toxic substances commonly encountered and to be along with lead the toxic substances adversely affecting the largest numbers of people (276). Mercury in the presence of other metals in the oral environment undergoes galvanic action, causing movement out of amalgam and into the oral mucosa and saliva (174, 183, 192, 436, 199). Mercury in solid form is not stable due to its vapor pressure and oral galvanism of mixed metals so that it evaporates continuously from amalgam fillings in the mouth, being transferred over a period of time to the host (49, 79, 83, 85, 183, 199, 335, etc.). The daily total exposure of mercury from fillings is from 3 to 1000 micrograms per day, with the average exposure for those with several fillings being above 30 micrograms per day and the average uptake over 7 μg/day (49, 183, 199, 79, 83, 85, 335, 603, etc.), with the majority of the rest excreted through the feces and often being over 30 μg/day (79, 335, 603). The average amount of mercury in the feces of a group with amalgams was over 10 times that of controls (79, 603). A 2009 study found that inorganic mercury levels in people have been increasing rapidly in recent years (543b). It used data from the U.S. Centers for Disease Control and Prevention's National Health Nutrition Examination Survey (NHANES) finding that while inorganic mercury was detected in the blood of 2 percent of women aged 18 to 49 in the 1999-2000 NHANES survey, that level rose to 30 percent of women by 2005-2006. Surveys in all states using hair tests have found dangerous levels of mercury in an average of 22 % of the population, with over 30% in some states like Florida and New York (543c). A large U.S. Centers for Disease Control epidemiological study, NHANES III, found that those with more amalgam fillings (more mercury exposure) have significantly higher levels of chronic health conditions (543a).

Amalgam fillings are the *largest source of mercury*[1] in most people with daily exposures documented to commonly be above government health guidelines (49, 79, 183, 199, 506, 594, 600, 607, 217). This is due to continuous vaporization of mercury from amalgam in the mouth, along with galvanic currents from mixed metals in the mouth that deposit the mercury in the gums and oral cavity (605). Due to the high daily mercury exposure and excretion into home and business sewers of those with amalgam, dental amalgam is also the largest source of the high levels of mercury found in all sewers and sewer sludge, and thus according to government studies a significant source of mercury in rivers, lakes, bays, fish, and crops (603). People also get significant exposure from vaccinations, fish, and dental office vapor (600).

When amalgam was placed into teeth of monkeys and rats, within one year mercury was found to have accumulated in the brain, trigeminal ganglia, spinal ganglia, kidneys, liver, lungs, hormone glands, and lymph glands (20). People also commonly get exposures to mercury and other toxic metals such as lead, arsenic, nickel, and aluminum from food, water, and other sources (600, 601). All of these are highly neurotoxic and are documented to cause neurological damage which can result in chronic neurological conditions over time, as well as ADHD, mood, and behavioral disorders (594, 600, 601, 577).

Another major source of mercury exposure is vaccines such as flu vaccines which have large amounts of mercury and aluminum, and have been linked to conditions like depression, Parkinson's, ALS, and dementia (445, 585, 598). It has been found that vaccines contain adjuvants like aluminum plus mercury thimerosal which overstimulate the immune system and brain, causing high levels of inflammation over long periods of time. There is evidence of a link between the aluminum hydroxide in vaccines, and symptoms associated with Alzheimer's, Parkinson's, and ALS(585). It has been found that those who get at least 5 flu shots have an increased risk of inflammatory conditions like Alzheimer's of at least 500%.

Mercury is one of the most toxic substances in existence and is known to bioaccumulate in the body of people and animals that have chronic exposure (85, 600, 577, 594). Mercury exposure is cumulative and comes primarily from 4 main sources: mercury amalgam dental fillings, food (mainly fish), vaccinations, and occupational exposure. Whereas mercury exposure from fish is primarily methyl mercury and mercury from vaccinations is thimerosal (ethyl mercury), mercury from occupational exposure and dental fillings is primarily from elemental mercury vapor. However bacteria, yeasts, and Vitamin B12 methylate inorganic mercury to methyl mercury in the mouth and intestines (607, 505) and mercury inhibits functional methylation in the body, a necessary process (504). Developmental and neurological conditions occur at lower levels of exposure from mercury vapor than from inorganic mercury or methyl mercury (606). Mercury in amalgam fillings, because of its low vapor pressure and galvanic action with other metals in the mouth, has been found to be continuously vaporized and released into the body, and has been found to be the directly correlated to the number of amalgam surfaces and the largest source of mercury in the majority of people (49, 183, 199, 209, 79, 99, 600), typically between 60 and 90% of the total. The level of daily exposure of those with several amalgam fillings commonly exceeds the U.S. EPA health guideline for daily mercury exposure of 0.1 μg/kg body weight/day, and the oral mercury level commonly exceeds the mercury MRL of the U.S.ATSDR of 0.2 μg/ cubic meter of air (217, 600). When amalgam fillings are replaced, levels of mercury in the blood, urine, and feces typically rise temporarily but decline between 60 to 85% within 6 to 9 months (79, 600).

1.2 Cytotoxic, neurotoxic, and immunotoxic effects of mercury

Mercury vapor from amalgam readily crosses cell membranes and binds to the -SH (sulphydryl) groups, resulting in inactivation of sulfur processes and blocking of enzyme functions such as cys-

[1] **Informativo:** "Dental Amalgam Mercury Solutions".

teine dioxygenase (CDO), sulfite oxidase, and gamma-glutamyltraspeptidase (GGC), producing sulfur metabolites with extreme toxicity that the body is unable to properly detoxify (33, 111, 114, 194, 258, 330, 331, 333), along with a deficiency in sulfates required for many body functions. Sulfur is essential in enzymes, hormones, nerve tissue, and red blood cells. These exist in almost every enzymatic process in the body. Blocked or inhibited sulfur oxidation at the cellular level has been found in most with many of the chronic degenerative diseases, including Parkinson's, Alzheimer's, ALS, MS, lupus, rheumatoid arthritis, MCS, etc (330, 331, 33, 35, 56, 194, 258), and appears to be a major factor in these conditions. The deficiency in conjugation and detoxification of sulfur based toxins in the liver results in toxic metabolites and progressive nerve damage over time (331). Mercury also blocks the metabolic action of manganese and the entry of calcium ions into cytoplasm (333). Oxidative stress and reactive oxygen species (ROS) have also been implicated as major factors in neurological disorders including stroke, PD, Alzheimer's, ALS, etc. (13, 56, 84, 169, 207b, 424, 442, 453, 462).

Programmed cell death (apoptosis) is documented to be a major factor in degenerative neurological conditions like ALS, Alzheimer's, MS, Parkinson's, etc. Some of the factors documented to be involved in apoptosis of neurons and immune cells include inducement of the inflamatory cytokine Tumor Necrosis Factor-alpha (TNFa) (126), reactive oxygen species and oxidative stress (13, 43a, 56a, 296b, 495), reduced glutathione levels (56, 126a, 111a), liver enzyme effects and inhibition of protein kinase C and cytochrome P450(43, 84, 260), nitric oxide and peroxynitrite toxicity (43a, 521, 524), excitotoxicity and lipid peroxidation (490, 496, 593), excess free cysteine levels (56d, 111a, 33, 330), excess glutamate toxicity (13b, 416, 445, 593, 598), excess dopamine toxicity (56d, 13a), beta-amyloid generation (462), increased calcium influx toxicity (296b, 333, 416, 432, 462c, 507) and DNA fragmentation (296, 42, 114, 142) and mitochondrial membrane dysfunction (56defg, 416, 444d).

The mechanisms by which mercury causes all of these conditions and neuronal apoptosis are documented in this review (often *synergistically*[2] along with other toxic exposures).

Chronic neurological conditions such as Alzheimer's appear to be primarily caused by chronic or acute brain inflammation. The brain is very sensitive to inflammation. Disturbances in metabolic networks: e.g., immuno-inflammatory processes, insulin-glucose homeostasis, adipokine synthesis and secretion, intra-cellular signaling cascades, and mitochondrial respiration have been shown to be major factors in chronic neurological conditions (592, 593, 598, 56g). Inflammatory chemicals such as mercury, aluminum, and other toxic metals as well as other excitotoxins including MSG and aspartame cause high levels of free radicals, lipid peroxidation, inflammatory cytokines, and oxidative stress in the brain and cardiovascular systems (13, 585, 593, 595-598) Acetylcholine depletion has been found to be a major factor in Alzheimer's, and aluminum has been found to inhibit choline transport and reduce neuronal choline acetyltransferase, which can lead to acetylcholine deficiency (580).

The brain has elaborate protective mechanisms for regulating neurotransmitters such as glutamate, which is the most abundant of all neurotransmitters. When these protective regulatory mechanisms are damaged or affected, chronic neurological conditions such as Alzheimer's can result (593). Mercury and other toxic metals inhibit astrocyte function in the brain and CNS(119), causing increased glutamate and calcium related neurotoxicity (119, 333, 416, 496, 593). Mercury and increased glutamate activate free radical forming processes like xanthine oxidase which produce oxygen radicals and oxidative neurological damage (142, 13). Nitric oxide related toxicty caused by peroxynitrite formed by the reaction of NO with superoxide anions, which results in nitration of tyrosine residues in neurofilaments and manganese Superoxide Dimustase (SOD) has been found to cause inhibition of the mitochondrial respiratory chain, inhibition of the glutamate transporter, and glutamate-induced neurotoxicity involved in ALS (524, 521, 56g).

[2]**Internet:** "http://www.flcv.com/synergis.html".

These inflammatory processes damage cell structures including DNA, mitochondria, and cell membranes. They also activate microglia cells in the brain, which control brain inflammation and immunity. Once activated, the microglia secrete large amounts of neurotoxic substances such as glutamate, an excitotoxin, which adds to inflammation and stimulates the area of the brain associated with anxiety (593, 598). Inflammation also disrupts brain neurotransmitters resulting in reduced levels of serotonin, dopamine, and norepinephrine. Some of the main causes of such disturbances that have been documented include vaccines, mercury, aluminum, other toxic metals, MSG, aspartame, etc. (585, 593, 598, 600, etc.)

Programmed cell death (apoptosis) is documented to be a major factor in degenerative neurological conditions like ALS, Alzheimer's, MS, Parkinson's, etc. Some of the factors documented to be involved in apoptosis of neurons and immune cells include mitochondrial membrane dysfunction (56bc, 416). Mitochondrial DNA mutations or dysfunction is fairly common, found in at least 1 in every 200 people (275), and toxicity effects affect this population more than those with less susceptibility to mitochondrial dysfunction. Mercury depletes GSH and damages cellular mitochrondria, which along with the increased lipid peroxidation in protein and DNA oxidation in the brain appears to be major factors in conditions such as autism, Parkinson's disease, Alzheimer's, etc. (33, 56, 416, 442, 56g). Some prevention and repair of such damage to mitochondria has been documented using pyroquinoline quinine (PQQ) (56g).

Reduced levels of magnesium and zinc are related to metabolic syndrome, insulin resistance, and brain inflammation and are protective against these conditions (595, 43). Mercury and cadmium inhibiting magnesium and zinc levels as well as inhibiting glucose transfer are other mechanisms by which mercury and toxic metals are factors in metabolic syndrome and insulin resistance/diabetes (43, 198, 338, 597).

TNFa (tumor necrosis factor-alpha) is a cytokine that controls a wide range of immune cell response in mammals, including cell death (apoptosis) in neuronal and immune cells. This process is involved in inflamatory and degenerative neurological conditions like ALS, MS, Parkinson's, rheumatoid arthritis, etc. Cell signaling mechanisms like sphingolipids are part of the control mechansim for the TNFa apoptosis mechanism (126a, 598). Gluthathione is an amino acid that is a normal cellular mechanism for controlling apoptosis. When glutathione is depleted in the brain, reactive oxidative species increased, and CNS and cell signaling mechinsisms are disrupted by toxic exposures such as mercury, neuronal cell apoptosis results and neurological damage. Mercury has been shown to induce TNFa and deplete glutathione, causing inflamatory effects and cellular apoptosis in neuronal and immune cells (126b, 126c).

Mercury's biochemical damage at the cellular level include DNA damage, inhibition of DNA and RNA synthesis (42, 114, 142, 197, 296, 392); alteration of protein structure (33, 111, 114, 194, 252, 442); alteration of the transport of calcium (333, 43b, 254, 263, 416, 462, 507); inhibitation of glucose transport (338, 254), and of enzyme function, protein transport, and other essential nutrient transport (96, 198, 254, 263, 264, 33, 330, 331, 339, 347, 441, 442); induction of free radical formation (13a, 43b, 54, 405, 424), depletion of cellular gluthathione (necessary for detoxification processes) (111, 126, 424), inhibition of glutathione peroxidase enzyme (13a, 442), inhibits glutamate uptake (119, 416, 445), induces peroxynitrite and lipid peroxidation damage (521b), causes abnormal migration of neurons in the cerebral cortex (149), immune system damage (34, 111, 194, 226, 252, 272, 316, 325, 355); and inducement of inflamatory cytokines (126, 181). Homocysteine has been found to facilitate and increase mercury toxicity (19c).

Na(+), K(+)-ATPase is a transmembrane protein that transports sodium and potassium ions across cell membranes during an activity cycle that uses the energy released by ATP hydrolysis. Mercury is documented to inhibit Na(+), K(+)-ATPase function at very low levels of exposure (288ab). Studies have found that in Alzheimer's cases there was a reduction in serum magnesium and RBC membrane Na(+)-K+ ATPase activity and an elevation in plasma serum digoxin (263).

The activity of all serum free-radical scavenging enzymes, concentration of glutathione, alpha tocopherol, iron binding capacity, and ceruloplasmin decreased significantly in Alzheimer's, while the concentration of serum lipid peroxidation products and nitric oxide increased. The inhibition of Na+-K+ ATPase can contribute to increase in intracellular calcium and decrease in magnesium, which can result in 1) defective neurotransmitter transport mechanism, 2) neuronal degeneration and apoptosis, 3) mitochondrial dysfunction, 4) defective golgi body function and protein processing dysfunction. It is documented in this paper that mercury is a cause of most of these conditions seen in Alzheimer's (13a, 111, 288, 442, 521b, 43, 56, 263, etc.)

Autoimmunity has also been found to be a factor in chronic degenerative autoimmune conditions such as ALS, with genetic *susceptibility*[3] a major factor in who is affected. One genetic factor in Hg induced autoimmunity is major histocompatibility complex (MHC) linked. Both immune cell type Th1 and Th2 cytokine responses are involved in autoimmunity (425c). One genetic difference found in animals and humans is cellular retention differences for metals related to the ability to excrete mercury (426). For example it has been found that individuals with genetic blood factor type APOE-4 do not excrete mercury readily and bioaccumulate mercury, resulting in susceptibility to chronic autoimmune conditions such as Alzheimer's, Parkinson's, etc. as early as age 40(437b), whereas those with type APOE-2 readily excrete mercury and are less susceptible (437, 35). Those with type APOE-3 are intermediate to the other 2 types. The incidence of autoimmune conditions have increased to the extent this is now one of the leading causes of death among women (450). Also when a condition has been initiated and exposure levels decline, autoimmune antibodies also decline in animals or humans (233, 234c, 60, 369, 405)

Mercury has been found in autopsy studies to accumulate in the brain of those with chronic exposures, and levels are directly proportional to the number of amalgam filling surfaces (85, 577). Dozens of studies have documented that exposure to inorganic mercury causes memory loss and memory problems (435, 600). Mercury has been found to cause memory loss by inactivating enzymes necessary for brain cell energy production and proper assembly of the protein tubulin into microtubules (258). In a recent study, mercury at extremely low levels found commonly in those with amalgam fillings was found to disrupt membrane structure and linear growth rates of neurites in most nerve growth cones exposed, causing tubulin/micortubile structure to disintegrate. The study also found that mercury also interferes with formation of tubulin producing neurofibrillary tangles in the brain similar to those observed in Alzheimers patients (207, 462, 594), as well as causing neuronal somata to fail to sprout. The process was found to result in low levels of zinc in the brain (158, 43). There is evidence that certain redox active metal ions including copper and mercury are important in exacerbating and perhaps facilitating Abeta-mediated oxidative damage and amyloid deposits in Alzheimer's disease (462, 488, 590, 594). Mercury has also been shown to induce cell cytotoxicity and oxidative stress and increases beta-amyloid secretion and tau phosphorylation in neuroblastoma cells resulting in amyloid plaques which is found in Alzheimer's patients, and to also cause the formation of the neurofibrilla tangles found in the Alzheimer's patient brain (462, 258). Mercury and the induced neurofibrillary tangles also appear to produce a functional zinc deficiency in the of AD sufferers (242), as well as causing reduced lithium levels which is another factor in such diseases. Lithium protects brain cells against excess glutamate induced excitability and calcium influx (280, 416, 445, 56). These studies clearly implicate mercury as having the ability to cause neurodegeneration in the brain and CNS, at levels of 20 ppb, which is lower than that of many with several amalgam fillings or dental occupational exposure (462). Researchers at Geriatric and Psychiatric Univ. Clinics in Basel, Switzerland concluded that inorganic mercury appears to be a causative factor in Alzheimer's and the Swizz Dental Assoc. recommended avoidance of amalgam use in those with neurological disorders (462). Clinical experience has also found that DMSO has some ability to repair tubulin damage (594).

[3]**Informativo:** "Susceptibility Factors in Mercury Toxicity: Immune Reactivity, Detoxification System Function, Enzymatic Blockages, Synergistic Exposures".

Clinical tests of patients with MND, ALS, Parkinson's, Alzheimer's, Lupus (SLE), rheumatoid arthritis and autism have found that the patients generally have elevated plasma cysteine to sulphate ratios, with the average being 500% higher than controls (330, 331, 56, 33d), and in general being poor sulphur oxidizers. This means that these patients have insufficient sulfates available to carry out necessary bodily processes and that cysteine levels build up in the brain and CNS to neurotoxic levels. Mercury has been shown to diminish and block sulphur oxidation and thus reducing glutathione levels which is the part of this process involved in detoxifying and excretion of toxics like mercury (33). Glutathione is produced through the sulphur oxidation side of this process. Low levels of available glutathione have been shown to increase mercury retention and increase toxic effects (111), while high levels of free cysteine have been demonstrated to make toxicity due to inorganic mercury more severe (333, 194, 56, 33d). Mercury has also been found to play a part in inducing intolerance and neuronal problems through blockage of the P-450 enzymatic process (84, 33d).

Mercury also blocks the immune function of magnesium and zinc (198, 427, 43, 38), whose deficiencies are known to cause significant neurological effects (461, 463, 443). The low Zn levels result in deficient CuZnSuperoxide dismustase (CuZnSOD), which in turn leads to increased levels of superoxide due to toxic metal exposure (443). Mercury is known to damage or inhibit SOD activity (33, 111). Mercury induced lipid peroxidation has been found to be a major factor in mercury's neurotoxicity, along with leading to decreased levels of glutathione peroxidation and superoxide dismustase (SOD)(13, 254, 489, 494-496).

Mercury inhibits sulfur ligands in MT and in the case of intestinal cell membranes inactivates MT that normally bind cuprous ions (477), thus allowing buildup of copper to toxic levels in many and malfunction of the Zn/Cu SOD function. Modern amalgams commonly used in the U.S. have higher levels of copper than the traditional silver amalgams and result in much higher exposure levels to mercury and copper (258). This is a factor in higher incidence of neurodegnerative condidtions like Alzheimer's. Exposure to mercury results in changes in metalloprotein compounds that have genetic effects, having both structural and catalytic effects on gene expression (114, 241, 296, 442, 464, 477, 495). Some of the processes affected by such MT control of genes include cellular respiration, metabolism, enzymatic processes, metal-specific homeostasis, and adrenal stress response systems. Significant physiological changes occur when metal ion concentrations exceed threshold levels.

Copper is an essential trace metal which plays a fundamental role in the biochemistry of the nervous system (489, 495, 464). Several chronic neurological conditions involving copper metabolic disorders are well documented like Wilson's Disease and Menkes Disease. Mutations in the copper/zinc enzyme superoxide dismustase (SOD) have been shown to be a major factor in the motor neuron degeneration in conditions like familial ALS and similar effects on Cu/Zn SOD to be a factor in other conditions such as autism, Alzheimer's, Parkinson's, and non-familial ALS (489, 495, 464, 111). This condition can result in zinc deficient SOD and oxidative damage involving nitric oxide, peroxynitrite, and lipid peroxidation (495, 496, 489), which have been found to affect glutamate mediated excitability and apoptosis of nerve cells and effects on mitochondria (416, 445, 495, 496, 119) These effects can be reduced by zinc supplementation (464, 495, 517), as well as supplementation with antioxidants and nitric oxide-suppressing agents and peroxynitrite scavengers such as Vit C, Vit E, lipoic acid, Coenzyme Q10, carnosine, gingko biloba, N-acetylcysteine, turmeric, etc.(444, 464, 494, 495, 469, 497). Some of the antioxidants were also found to have protective effects through increasing catalase and SOD action, while reducing lipid peroxidations (494a). Curcumin as an antioxidant, anti-inflammatory and lipophilic action improves the cognitive functions in patients with AD (497). A growing body of evidence indicates that oxidative stress, free radicals, beta amyloid, cerebral deregulation caused by bio-metal toxicity and abnormal inflammatory reactions contribute to the key event in Alzheimer's disease pathology. Due to various effects of curcumin, such as decreased Beta-amyloid plaques, delayed degradation of neurons, metal-chelation, anti-inflammatory, antioxidant and decreased microglia formation, the overall memory in patients with AD has improved. Ceruloplasmin in plasma can be similarly affected by copper metabolism disfunction, like

SOD function, and is often a factor in neurodegeneration (489).

Studies showed that metals can induce A-beta aggregation and toxicity and are concentrated in Alzheimer's brain. There is accumulating evidence that interactions between beta-amyloid and copper, iron, and zinc are associated with the pathophysiology of Alzheimer's disease (AD) (590). A significant dyshomeostasis of copper, iron, and zinc has been detected, and the mismanagement of these metals induces beta-amyloid precipitation and neurotoxicity. Chelating agents offer a potential therapeutic solution to the neurotoxicity induced by copper and iron dyshomeostasis. Currently, the copper and zinc chelating agents clioquinol and desferroxamine represent a potential therapeutic route that may not only inhibit beta-amyloid neurotoxicity, but may also reverse the accumulation of neocortical beta-amyloid. There is also evidence that melatonin and curcumin may have beneficial effects on reducing metal toxicity (591, 497). Turmeric/curcumin has been found to reduce some of the toxic and inflammatory effects of toxic metals (497, 498).

Low levels of mercury and toxic metals have been found to inhibit dihydroteridine reductase, which affects the neural system function by inhibiting transmitters through its effect on phenylalanine, tyrosine and tryptophan transport into neurons (122, 257, 289, 342, 372). This was found to cause severe impaired amine synthesis and hypokinesis. Tetrahydrobiopterin, which is essential in production of neurotransmitters, is significantly decreased in patients with Alzheimer's's, Parkinson's, MS, and autism. Such patients have abnormal inhibition of neurotransmitter production.

Some studies have also found persons with chronic exposure to electromagnetic fields (EMF) to have higher levels of mercury exposure and excretion (38). Magnetic fields are known to induce current in metals and would increase the effects of galvanism. Occupational exposure to higher levels of EMF have also been found in many studies to result in much higher risk of chronic degenerative neurological conditions such as ALS (39) and Alzheimer's Disease (40) Since EMF causes increased mercury exposure in those with amalgam, and mercury is also known to cause these conditions, again it is not clear the relative importance of the factors since the studies were not controlled for mercury levels or number of amalgam fillings. Studies have also found a correlation between high levels of aluminum exposure and dementia such as Alzheimer's (470, 580), and concluded based on extensive literature that the neurotoxic effects of aluminium are beyond any doubt, and aluminium as a factor in some AD cannot be discarded (470b). It is well documented that neurological effects of toxics are *synergistic*[4]. Flu shots have mercury and aluminum which both are known to accumulate in the brain over time. A study of people who received flu shots regularly found that if an individual had five consecutive flu shots between 1970 and 1980 (the years studied) his/her chances of getting Alzheimer's Disease is ten times higher than if they had one or no shots (475).

Many studies of patients with major neurological or degenerative diseases have found evidence amalgam fillings may play a major role in development of conditions such as such as Alzheimer's (66, 67, 158, 166, 204, 207, 221, 238, 242, 244, 257, 300, 303, 369, 444d, 462, 35, 38d) and significantly improve after dental amalgam replacement and dental infection cleanup. Low levels of toxic metals have been found to inhibit dihydroteridine reductase, which affects the neural system function by inhibiting brain transmitters through its effect on phenylalanine, tyrosine and tryptophan transport into neurons (122, 257, 289, 372). This was found to cause severe impaired amine synthesis and hypokinesis. Tetrahydro-biopterin, which is essential in production of neurotransmitters, is significantly decreased in patients with Alzheimer's's, Parkinson's, and MS. Such patients have abnormal inhibition of neurotransmitter production.(supplements which inhibit breach of the blood brain barrier such as bioflavonoids have been found to slow such neurological damage).

Also mercury binds with cell membranes interfering with sodium and potassium enzyme functions, causing excess membrane permeability, especially in terms of the blood-brain barrier (155, 207, 311). Less than 1ppm mercury in the blood stream can impair the blood- brain barrier. Mercury was also found to accumulate in the mitochondria and interfere with their vital functions, and to inhibit

[4]**Internet:** "http://www.flcv.com/synergis.html".

cytochrome C enzymes which affect energy supply to the brain (43, 84, 232, 35). Persons with the APO-E4 gene form of apolipoprotein E which transports cholesterol in the blood, are especially susceptible to this damage (207, 221, 346, 437, 580), while those with APO-E2 which has extra cysteine and is a better mercury scavenger have less damage. The majority have an intermediate form APO-E3. This appears to be a factor in *susceptibility*[5] to Alzheimer's disease, Parkinson's disease and multiple sclerosis (291). Ones susceptibility can be estimated by testing for this condition. Repeated exposure to pesticides has also been found to increase Alzheimer's Disease risk (586).

A major systematic review of all medical studies found on the connection of mercury exposure and Alzheimer's Disease was recently carried out by MDs and PhDs. (435) Studies were screened according to a pre-defined protocol. The author's noted that mercury is one of the most toxic substances known to humans and in addition to being widespread in the environment has also been used extensively in vaccinations and dental amalgam. Studies were screened according to a pre-defined protocol. Most of the studies testing memory in individuals exposed to inorganic mercury (IM), found significant memory deficits. Some autopsy studies found increased mercury levels in brain tissues of AD patients. "In vitro models showed that IM reproduces all pathological changes seen in AD, and in animal models IM produced changes that are similar to those seen in AD. Its high affinity for selenium and selenoproteins suggests that IM may promote neurodegenerative disorders via disruption of redox regulation." IM appears to play a role as a co-factor in the development of AD. It appears to also increase the pathological influence of other metals through adverse effects on the blood brain barrier. Our mechanistic model describes potential causal pathways. It concludes: "As the single most effective public health primary preventive measure, industrial, and medical usage of mercury should be eliminated as quickly as possible."

"Earlier research on the biochemical abnormalities of the Alzheimer's Diseased (AD) brain showed that mercury, and only mercury, at very low levels induced the same biochemical abnormalities when added to normal human brain homogenates or in the brains of rats exposed to mercury vapor." (438) "Since the brain is more vulnerable to oxidative stress than any other organ, it is not surprising that mercury, which promotes oxidative stress, is an important risk factor for brain disorders."

1.3 Insulin resistance as a factor in Alzheimer's

Higher insulin and glucose levels in the blood and deficiency of glucose in brain cells that need it has been found to lead to neurological problems such as Alzheimer's (580, 581). Those with either type I or type II diabetes have been found to be more likely to have other chronic conditions including heart disease, strokes, kidney disease, Alzheimer's, eye conditions and blindness (580, 581). Diabetes also impacts memory by increasing the risk blood vessels will become obstructed, restricting blood flow to the brain. High blood glucose levels also impact cognition through formation of sugar-related toxins called advanced glycation end products (AGEs). AGEs have been found to be a factor in aging, diabetes, and Alzheimer's. Glycotoxins are formed when sugars interact with proteins and lipids, damaging the structure of proteins and membranes, rendering them less able to carry out their many vital processes. (581). Studies have shown that AGEs are a key factor in cross-linking of harmful beta-amyloid plaques in the brain that are implicated in Alzheimer's. As previously documented mercury and aluminum exposure increase insulin resistance and amalgam replacement and detoxification reduce insulin resistance.

Inflammation induced by vaccine adjuvants like aluminum and mercury or by excitotoxins like MSG has been found to play a significant role in insulin resistance (type-2 diabetes) and in high levels of LDL cholesterol (597, 598, 585, 593). Reduced levels of magnesium and zinc are related to metabolic syndrome, insulin resistance, and brain inflammation, and these are protective against

[5]**Informativo:** "Susceptibility Factors in Mercury Toxicity: Immune Reactivity, Detoxification System Function, Enzymatic Blockages, Synergistic Exposures".

these conditions (599, 43). Mercury and cadmium by inhibiting magnesium and zinc levels as well as inhibiting glucose transfer are other mechanisms by which mercury and toxic metals are factors in metabolic syndrome and insulin resistance/diabetes (43, 198, 338, 597). Mercury inhibits production of insulin and is a factor in diabetes and hypoglycemia, with significant reductions in insulin need after replacement of amalgam filings and normalizing of blood sugar (35, 502). Iron overload has also been found to be a cause of insulin resistance/type 2 diabetes (582).

1.4 Treatment of Alzheimer's

In some cases replacement of amalgam fillings or toxic metals chelation has been found to result in cure or significant improvement in Alzheimer's patients (204, 35, 38c). Alzheimer's patients commonly are found to be deficient in omega 3 fatty acids, vit C, B12, SAMe, vit K, etc. and clinical experience has found supplementing these to be beneficial in some cases (580). A study demonstrated protective effects of methylcobalamin, a vitamin B12 analog, against glutamate- induced neurotoxicity (503), and similarly for iron in those who are iron deficient . Supplements with clinical experience indicating benefit in many Alzheimer's/dementia cases include pantothenic acid (B5), vit B12, vit B1, vit B6, Vit E, Ginkgo Biloba, Vit C, Acetyl-L-Carnatine, CoQ10, EFAs (DHA/EPA), N-Acetyl-Cysteine (NAC), SAMe, folate, inositol, melatonin, carnosine (580). Two treatments shown to be significantly beneficial in the majority of Alzheimer's patients using the supplement are Huperzine A and Kami-Umtan-To (KUT) (580). Lithium supplements (lithium carbonate and lithium oratate) have been found to be effective in protecting neurons and brain function from oxidative and excitotoxic effects. A recent study demonstrated that combined treatment with lithium and valproic acid elicits synergistic neuroprotective effects against glutamate excitotoxicity in cultured brain neurons (280).

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