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Evidence supporting a link between dental amalgams and chronic illness, fatigue, depression, anxiety, and suicide

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Abstract

The purpose of this review is to examine the evidence for a relationship between mercury (Hg) exposure from dental amalgams and certain idiopathic chronic illnesses – chronic fatigue syndrome (CFS), fibromyalgia (FM), depression, anxiety, and suicide. Dental amalgam is a commonly used dental restorative material that contains approximately 50% elemental mercury (Hg^0) by weight and releases Hg^0 vapor. Studies have shown that chronic Hg exposure from various sources including dental amalgams is associated with numerous health complaints, including fatigue, anxiety, and depression – and these are among the main symptoms that are associated with CFS and FM. In addition, several studies have shown that the removal of amalgams is associated with improvement in these symptoms. Although the issue of amalgam safety is still under debate, the preponderance of evidence suggests that Hg exposure from dental amalgams may cause or contribute to many chronic conditions. Thus, consideration of Hg toxicity may be central to the effective clinical investigation of many chronic illnesses, particularly those involving fatigue and depression.

1. INTRODUCTION

Mercury (Hg)-based amalgam is a commonly used dental restorative material, which was introduced in the western world in the 1830s, and which has been the subject of recurrent controversies due to its significant elemental mercury (Hg^0) content ever since (Bjørklund 1989). Amalgam restorations are euphemistically known as "silver fillings" even though their main constituent is Hg^0. By weight, today's dental amalgam is a mixture of about 50% Hg, 22–32% silver (Ag), 14% tin (Sn), and 8% copper (Cu), as well as other metals, depending on the type of amalgam (Brune 1986; Ferracane 2001). Each of these constituents may have toxic risks, but Hg^0 is the greatest concern because of its relatively high vapor pressure, i.e., high volatility, at body temperature. This property

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means that Hg^0 vapor, which is highly absorbable, is continuously released from the surfaces of any dental amalgam restoration.

According to Richardson *et al.* (2011), 181.1 million Americans carry a total of 1.46 billion restored teeth (based on 2001 to 2004 population statistics), and the majority of these restorations are amalgam. Further, children as young as 26 months receive these dental restorations. Richardson *et al.* (2011) conservatively estimate that approximately 67.2 million Americans have Hg^0 exposures that exceed the Hg^0 dose associated with the reference exposure level (REL) of 0.3 μg Hg^0/m^3 established by the US Environmental Protection Agency (EPA); and 122.3 million Americans exceed the dose associated with the REL of 0.03 μg Hg^0/m^3 established by the California Environmental Protection Agency (CalEPA 2008; EPA 1995). Although amalgam use may be on the decline, it still constitutes 45% of dental restorations worldwide (Heintze and Rousson 2012). In the US, according to a survey reported in 2011, the use of amalgam varies widely by region, and most dentist-respondents still use amalgam rather than composite for posterior (molar) restorations (Makhija *et al.* 2011).

Norway and Sweden have banned amalgam, reportedly due to environmental concerns. Specifically, Norway introduced a general ban on the use of Hg in commercial products in 2008 (Ministry of the Environment 2007); and the placement of new dental amalgam fillings was totally banned at the end of 2010 after a three-year exemption for some patient groups. Sweden has banned the use of amalgam after June 1, 2009, except for permitting a limited exemption for special medical reasons (Swedish Chemicals Agency 2008–2012). Germany and Canada both advise against placing amalgam in pregnant women and children (US Public Health Service 1997).

Numerous studies suggest that exposure to Hg^0 from amalgam fillings may affect physical and mental health. The purpose of this review is to examine key symptoms of Hg toxicity in comparison to key symptoms of certain idiopathic chronic illnesses, as well as reports of successful treatments, in order to evaluate the likelihood that Hg plays a role in such illnesses.

2. MERCURY EXPOSURE FROM DENTAL AMALGAM FILLINGS

2.1. Exposure and absorption

Dental patients are exposed to the Hg used in dental restorative materials primarily via vapor (Agency for Toxic Substances and Disease Registry (ATSDR) 1999), which is both absorbed by the oral cavity and inhaled into the lungs. Additional exposure to Hg as well as to the other metals in dental amalgam occurs through metal corrosion products in swallowed saliva (Eneström & Hultman 1995), and erosion is also a contributing factor (Brune & Evje 1985). Dental amalgam fillings are the predominant source of human exposure to both Hg^0 vapor and ionic inorganic Hg for the general population (Clarkson *et al.* 1988). Dental amalgams also can be a source of organic Hg generated by microbes in the gastrointestinal tract that are exposed to available inorganic Hg (Gilmour *et al.* 2013).

2.2. Blood, urine, intraoral Hg levels correlate with the extent of amalgam restorations

Hg exposure from dental amalgam fillings, as measured by levels in blood, urine, and intraoral air, is correlated with the extent of amalgam restorations as reported by several groups in different countries. For example, Abraham, Svare, and Frank (1984) found that blood Hg concentrations were positively correlated with the number and surface area of amalgam fillings in a study of 47 persons with and 14 persons without amalgam fillings.

Measuring intraoral air, Vimy and Lorscheider (1985) estimated that subjects with 12 or more occlusal amalgam surfaces received an average daily dose of 29 μg Hg, while the average dose for subjects with four or fewer occlusal amalgam surfaces was 8 μg Hg/day.

A significant positive correlation between urinary Hg levels and the extent of amalgam restorations, measured as number and size of fillings, has been found in several studies (Dunn *et al.* 2008; Olstad *et al.* 1987; Woods *et al.* 2007). For example, Dunn *et al.* (2008) found a significant dose-response relationship between urinary Hg levels and the number of amalgam restorations in 534 schoolchildren. They also found that daily gum chewing in the presence of amalgam was associated with high urinary Hg levels.

Similarly, derived from the data from a study by Woods *et al.* (2007) of 507 schoolchildren, Geier *et al.* (2012) found a significant dose-response relationship between urinary Hg levels and an exposure variable based on size and age of amalgam restorations. There is also a significant positive correlation between urinary Hg levels and the time since placement (Woods *et al.* 2007).

It has also been reported that cyclic loading (e.g., chewing) strongly promoted degradation of the amalgam surface, yielding corrosion particulates in the saliva environment. Corrosion products were found to be loosely bound on the amalgam surface and could be removed by brushing similar to tooth brushing. The daily release of ionic Hg was estimated at approximately 3 μg/cm^2 (Brune & Evje 1985).

Incidentally, although urine or blood Hg levels appear to reflect recent exposure to Hg on a population basis, this relationship may not hold for some individuals who may have a predisposition to retain Hg (Mutter *et al.* 2007). Furthermore, neither urine nor blood levels of Hg reflect body burden or toxicity (Berlin *et al.* 2007). Indeed, some individuals with a high Hg body burden may show low levels in blood, urine, and hair, apparently due to the body's biochemical Hg-detoxification processes becoming impaired, leading to increased retention (Mutter *et al.* 2007).

2.3. Mercury concentrates in tissues

Elementary Hg vapor from dental amalgam is well absorbed in the oral cavity and the lungs (Berlin *et al.* 2007). Following uptake by blood and tissue cells, the neutral Hg atoms (Hg^0) are oxidized to divalent Hg (Hg^{2+}). Before such oxidation takes place, a portion of the neutral Hg atoms may cross the blood-brain barrier (and the placenta), where they are oxidized to the divalent (lipophobic) form and thus accumulate in target tissues (Clarkson 1989). Animal studies in sheep and monkeys confirm the accumulation of Hg in tissues following amalgam placement (Lorscheider *et al.* 1995a). In addition, several human autopsy studies, described below, show an association between amalgams and tissue Hg levels.

2.4. Amalgams and kidney Hg levels

In toxicology, a critical organ is defined as an organ where those pathological changes that are easily observable first develop. The brain and the kidneys are considered critical organs for Hg exposure (Bjørklund 1991; International Programme on Chemical Safety (IPCS) 1991). Other tissue targets include the retina, thyroid, heart, lungs, and liver.

For example, in a study of Hg levels in living donor kidneys (n=109), Barregård *et al.* (2010) found that the number of amalgam surfaces was the main determinant of kidney Hg levels, and that these levels increased by about 6% for every additional amalgam surface. More recently, Geier *et al.* (2013) found a statistically significant dose-dependent correlation between cumulative exposure to dental amalgam (scored as small, medium or large fillings) and urinary levels of an isozyme of glutathione-*S*-transferase (GST-α), which is considered a biomarker of kidney damage.

2.5. Infant exposures correlate with the number of maternal amalgam fillings

A dose-dependent relationship has been observed between the number of maternal amalgam fillings and various measures of infant Hg exposure. For example, the number of maternal amalgam fillings has been found to be significantly associated with the levels of inorganic Hg and total Hg in cord blood (Palkovicova *et al.* 2008; Vahter *et al.* 2000) as well as the levels of inorganic Hg in the placenta (Ask *et al.* 2002). Mercury levels in amniotic fluid (Luglie *et al.* 2003) and breast milk (Drasch *et al.* 1998; Oskarsson *et al.* 1996) have also been found to be significantly correlated with the number of maternal amalgam fillings.

Post-mortem animal and human evidence suggests that maternal dental amalgam Hg is transferred to fetal organs in a dose-dependent manner. In a prospective animal study, Takahashi *et al.* (2001) implanted pregnant rats with a single amalgam restoration and found that the Hg concentrations in the placenta and the fetal organs were significantly greater than the corresponding Hg levels in the controls. Takahashi *et al.* (2003) then implanted pregnant rats with one, two, or four amalgam restorations and found a dose-dependent relationship between the number of amalgam fillings and the Hg concentrations in fetal as well as maternal organs. In a human autopsy study, Drasch *et al.* (1994) reported that the levels of Hg in cerebral cortex tissue samples of autopsied infants 11–50 weeks old (n=35) were significantly associated with the number of maternal amalgam fillings.

Interestingly, Holmes *et al.* (2003) measured hair Hg levels in autistic children and controls and found that the number of maternal amalgam fillings was significantly associated with the child's hair Hg levels in the controls, though not in the autistic children. (The major finding of this study was that hair Hg levels in autistic children are inversely correlated with severity of autism, suggesting that autistic children have impaired excretion of Hg.)

2.6. Autopsy findings

Post-mortem studies have also shown this same dependence of tissue Hg levels on the number or the surface area of the subjects' amalgam fillings. For example, in autopsies of 34 subjects, Friberg *et al.* (1986) found a statistically significant association between the concentration of inorganic Hg in the occipital lobe cortex and the number and surface area of amalgam fillings. More recently in a study of 18 cadavers, Guzzi *et al.* (2006) found that total Hg levels in all types of tissue were significantly higher in subjects with a greater number of occlusal amalgam surfaces (>12) compared with those with fewer (0–3). The authors also reported that the greater the number of amalgam fillings, the greater the likelihood that Hg was found in the brain. Indeed, Hg levels in the cerebral cortex and pituitary gland were more than ten times higher in subjects with more than 12 occlusal amalgam surfaces than in subjects with three or fewer (for both tissues, p-values = 0.0007). Finally, in autopsies of 30 subjects, Björkman *et al.* (2007) found that inorganic Hg levels in both the blood and occipital cortex, as well as total Hg in the pituitary and thyroid glands, were strongly associated with the subjects' number of dental amalgam surfaces at the time of death.

2.7. Porphyrins

Similar positive correlations between amalgam fillings and the levels and/or relative levels of certain urinary porphyrins have been observed. Porphyrins, which are intermediate metabolites on the heme synthesis pathway, have been shown to be biomarkers for the body burden of toxic metals or other toxicants that may accumulate under chronic, low-level exposures (Woods *et al.* 1996). Levels of certain porphyrins form a profile that is unique to each toxicant (Miller and Woods 1993; Woods *et al.* 1996).

Supporting the preceding observations, in a reanalysis of the Casa Pia children's amalgam trial dataset

(n=462), Geier *et al.* (2011) found a significant dose-dependent correlation between cumulative exposure to Hg from dental amalgams (as measured by the size of the fillings and years of exposure) and certain urinary porphyrins (pentacarboxyporphyrin, precoproporphyrin, and coproporphyrin). These findings are noteworthy because they suggest that Hg body burden is associated with amalgams – whereas, using a different approach, the original results (DeRouen *et al.* 2006) found no cause for concern.

3. MERCURY EXPOSURE AND CHRONIC ILLNESS

High levels of Hg exposure are known to cause serious health complaints (ATSDR 1999; Kokayi *et al.* 2006), but the effects of chronic, low-level exposures have been less clear. However, the recent identification of several genes that convey susceptibility to Hg toxicity (described below), as well as the identification of subtle but significant adverse health effects associated with chronic, low-dose Hg exposures, have raised the level of concern.

Unfortunately, chronic Hg toxicity has been difficult to study in populations, in part because no simple and reliable metric for exposure or body burden was available until recently (Mutter *et al.* 2004). Moreover, as those authors reported, the health effects of Hg exposures are varied and nonspecific, beginning subtlety and unfolding over years or decades. Finally, many as-yet-unidentified genetic factors may affect individuals, yet be masked in population studies (Mutter *et al.* 2004). Furthermore, interpretation of reported observations can be difficult because of co-exposures from other toxic metals, such as arsenic (As) and lead (Pb), and/or from toxic organic molecules such as chloroform and hydroquinone in the case of dental health personnel.

3.1. Exposures and illness in 9-11 first-responders

As an example of such co-exposures, Kokayi *et al.* (2006) found that uniformed service personnel and residents of lower Manhattan who were exposed to the air at Ground Zero following September 11, 2001 for extended periods of time reported serious illnesses. Most had at least eight health complaints, which included severe respiratory problems, digestive problems, skin rashes, sleeplessness, anxiety, depression, weight gain, elevated blood pressure, lethargy, and recurrent headaches. The authors reported that of those tested for heavy metal toxicity using a challenge urine test, 85% had excessively high levels of lead (Pb) and Hg. Chelation for heavy metals using dimercaptosuccinic acid (DMSA) was the primary treatment prescribed. After three to four months of treatment, the first cohort of 100 individuals reported significant (greater than 60%) improvement in all symptoms. However, in an event like this, it is not possible to discern the degree to which the observed health effects were caused by Hg versus Pb, unless external data can be used to estimate the relative contributions of each. Nor is it possible to discern to what extent the improvement was associated with the removal of Hg versus Pb.

3.2. Dental workers and illness

Studies show that dental health personnel who are occupationally exposed to Hg appear to suffer both a higher body burden of Hg and a higher total illness burden than is found in the general population (Duplinsky and Cichetti 2012; Martin, Naleway, and Chou 1995). For example, in a study of 41 dental assistants and 64 controls in Norway, Moen, Hollund, and Riise (2008) established that the dental assistants had significantly higher rates of neurological symptoms, psychosomatic symptoms, problems with memory and concentration, fatigue, and sleep disturbance than controls. Similarly, Hilt *et al.* (2009) found that dental assistants (n=608) had a relative risk of 2.0 for having five or more cognitive symptoms with a frequency of "often" or greater, relative to controls (n=425). More recently, Duplinsky and Cichetti (2012) reported that a representative sample of dentists (n=600) purchased significantly more illness-specific prescribed medications than controls who were matched for insurance-plan structure as well as gender, age, and geographical area, for the following disease categories: neuropsychological, neurological, respiratory, and cardiovascular.

3.3. Chronic fatigue syndrome

Chronic fatigue syndrome (CFS) is a distinctive syndrome characterized by prolonged fatigue and poor recovery after exertion, in combination with symptoms such as muscle pain, joint pain, headaches, tender lymph nodes, recurrent sore throat, and significant problems with concentration, memory and sleep. The CFS diagnosis is given only when the patient's symptoms have lasted for at least six months, and can only be made after various other etiologies of fatigue (except heavy metal intoxication, chronic viral infection, and Parkinson's disease) have been excluded (Fukuda *et al.* 1994). CFS may also be referred to as myalgic encephalomyelitis (ME), chronic fatigue immune dysfunction syndrome (CFIDS), postviral fatigue syndrome, or described by several other terms (Sharpe and Campling 2008). The etiology of CFS is unknown. The syndrome often results in severe functional limitation. The estimate for the prevalence of CFS varies from 0.4 to 2.5% in the general population of the USA and the UK (Prins *et al.* 2006).

Studies have shown that delayed-type hypersensitivities (type 4 allergy) to nickel (Ni) and Hg are more frequent in patients with CFS as compared to healthy controls. For example, Marcusson, Lindh, and Evengård (1999) patch-tested 50 patients with CFS and 73 controls and established that allergy to Ni occurred in 36% of patients versus 19% of controls ($p<0.05$). In females, the rate was 52% in patients versus 24% in controls ($p<0.05$).

Similarly, Regland *et al.* (2001) also found Ni allergy in a majority of women with CFS and muscle pain.

Furthermore, improvement in CFS symptoms following removal of dental amalgams has been reported. For example, Stejskal *et al.* (1999) investigated the effects of dental metal removal in 111 patients with metal hypersensitivity and symptoms resembling CFS. The presence of metal allergy was tested with the optimized lymphocyte transformation test, MELISA. A significant number of the patients, compared with 116 healthy subjects, had metal specific lymphocytes in the blood, with Ni being the most common sensitizer, followed by inorganic Hg, Ag, phenyl Hg, Cd, and palladium (Pd). The lymphocyte reactivity to metals decreased after dental metal removal, and 83 patients (76%) reported long-term health improvement, while 24 patients (22%) reported unchanged health, and two (2%) reported worsening of symptoms.

In addition, in a study of 248 patients with CFS-like symptoms, Yaqob *et al.* (2006) observed that most patients showed a positive lymphocyte response to Ni, and many showed a response to other metals including Hg. Following amalgam removal, the authors found that lymphocyte reactivity decreased significantly (defined as at least 30%) for 75% of the study subjects.

Earlier in 2004, Bates *et al.* conducted a study that addressed the allegations that amalgams are involved in nervous system disorders, such as multiple sclerosis, Alzheimer's disease, and CFS. The final cohort contained 20,000 people and the investigators found some evidence of an association between multiple sclerosis and amalgams, but no association with chronic fatigue syndrome. However, they used ICD-9: 780 which is not specific for CFS, but actually titled General Symptoms and includes several other conditions, such as coma, post vaccination fever, and convulsions.

3.4. Fibromyalgia

Fibromyalgia (FM) is a rheumatic disease with an unknown etiology and is characterized by widespread pain in 11 of 18 tender points experienced for at least three months (Wolfe *et al.* 1990). Symptoms of the disease include general fatigue, widespread musculoskeletal pain and stiffness, cognitive impairment, sleep disorders, and other symptoms that affect the quality of life (Arranz *et al.* 2010; Salaffi *et al.* 2009). Aside from musculoskeletal symptoms, FM has a considerable overlap in non-musculoskeletal symptoms with allied conditions such as CFS, tension headaches, migraine, affective disorders, and irritable bowel syndrome (Clauw 1995; Sivri *et al.* 1996). Like CFS, FM often leads to severe functional limitation. The estimated prevalence of FM is 0.5 to 6% in the general population of North America and Europe (Arranz *et al.* 2010; Branco *et al.* 2010; Lawrence *et al.* 2008; Wolfe *et al.* 2013).

Stejskal, Öckert, and Bjørklund (2013) studied the occurrence of allergy to Ni and other metals present in dental restorative materials in 15 female patients with primary FM in Sweden. All FM patients tested positive using MELISA to at least one of the metals present in their dental materials; the most frequent reactions were to Ni, inorganic Hg, Cd and Pb. Only a few of the 10 healthy controls reacted positively to inorganic Hg. Objective examination five years after amalgam removal showed that seven of the 15 patients (47%) no longer fulfilled the American College of Rheumatology 1990 criteria for FM; three others (20%) had improved; and five (33%) still had FM. The long-term health improvement in two-thirds of the FM patients in this study suggests that clinical metal allergy may be a risk factor in a large subset of FM patients.

3.5. Amalgam-associated ill health

Chronic Hg poisoning from dental amalgams is described in the toxicology literature, but is not generally recognized by physicians or institutions (Homme *et al.* 2014). Medical textbooks typically cover acute rather than chronic Hg poisoning and give no indication that dental amalgams may be a health risk (for example, Fauci 2008). Authorities including the US Food and Drug Administration have long claimed that dental amalgam poses no known risks to human health. In addition to these institutional biases, the idiosyncratic nature of Hg-related illnesses impedes diagnosis. Mercury-related illnesses present with a slow onset of wide-ranging, nonspecific, variable symptoms that lack a cohesive clinical picture (Gerstner & Huff 1977). Furthermore, no reliable diagnostic test exists for exposure or body burden (Berlin *et al.* 2007), aside from the relatively new porphyrins panel, which requires unusual care in handling of urine samples. Yet many physicians mistakenly exclude a diagnosis of chronic Hg poisoning based on low blood or urine Hg levels. For all these reasons, the literature on both amalgam illness and the effects of amalgam removal is sparse. Nonetheless, several Scandinavian studies, described below, have acknowledged amalgam illness and have also found that amalgam removal is associated with improvement in such symptoms.

For example, in a carefully controlled study, Stenman and Grans (1997), evaluated 311 patients who were suspected, by themselves or by a physician, of having amalgam-related illnesses, along with 37 healthy controls with and without amalgam fillings. Sixty patients were excluded due to low urinary Hg levels upon 2,3-Dimercapto-1-propanesulfonic acid (DMPS) challenge or due to clinical findings leading to another diagnosis (including multiple sclerosis and amyotrophic lateral sclerosis), leaving 251 patients with suspected amalgam illness, plus 37 healthy controls. All but 22 subjects then had their amalgam fillings removed if they had not already done so. At a follow-up of 1–3 years, 26 patients (10%) were subjectively and clinically cured. None of the 22 patients (9%) who still had amalgam fillings regarded themselves as cured. When the patents were classified according to urinary Hg levels upon DMPS

challenge, those in the highest quartile had an odds ratio of 7.2 for being cured following amalgam removal. The authors concluded that dental amalgams can cause clinical intoxication that may be curable upon amalgam removal. Incidentally, the results are consistent with the notion that the ability to excrete versus retain Hg may be an important factor not only in intoxication but also in recovery.

Similarly, in a study by Lindh *et al.* (2002), 796 patients suffering from a multitude of symptoms associated with metal exposure from dental amalgam and other metal alloys received a supportive antioxidant therapy plus removal of amalgam fillings. The researchers reported alleviation of symptoms and improvements in the quality of life in 70% of the patients.

More recently, in a study by Sjursen *et al.* (2011) of 40 patients claiming amalgam-associated illness, interviews of the 20 patients who underwent amalgam removal showed significant reductions in intra-oral and general health complaints at a three-year follow-up, whereas interviews of the 20 patients not receiving treatment did not.

The symptoms most commonly reported in patients with amalgam-associated ill health, either self-identified or physician-diagnosed as such, are also commonly reported in patients with CFS and FM, and are typified by depression and fatigue. Table 1 presents the most common symptoms in these three conditions and shows a high degree of overlap.

Tab. 1. List of the most common complaints in amalgam-associated ill health, chronic fatigue syndrome (CFS), and fibromyalgia.

Reported Symptoms	Associated with dental amalgams in chronically ill patients	CFS	Fibromyalgia
Chronic or periodic fatigue	✓	✓	✓
Depression	✓	✓	✓
Pain or discomfort in muscles	✓	✓	✓
Abnormal fatigue after physical exertion	✓	✓	✓
Impairment of concentration	✓	✓	✓
Impaired sleep	✓	✓	✓
Muscle discomfort in the whole body	✓	✓	✓
GI disturbance	✓	✓	✓
Frequent infections	✓	✓	✓
Aching lymph glands	✓	✓	✓
Sore throat	✓	✓	✓
Headache	✓	✓	✓
Impaired memory	✓	✓	✓

Not only are the symptoms of CFS and FM similar to those reported by patients associating their ill health with amalgam, but, as described above, several studies have shown that removal of amalgam fillings is associated with improvement in these symptoms in patients suffering from CFS and FM (Shin & Han 2012; Stejskal *et al.* 1999, Stejskal *et al.* 2013; Yaqob *et al.* 2006).

3.6. Depression, anxiety, and suicide

3.6.1. Effects of low-level Hg exposure on mood

The classic symptom of chronic Hg poisoning, known as erethism, is a personality change comprising excessive timidity, diffidence, shyness, loss of self-confidence, anxiety, a desire to remain unobserved and unobtrusive, a pathological fear of ridicule, and an explosive loss of temper when criticized (Clarkson & Magos 2006). Anxiety and depression are among the many nonspecific symptoms associated with chronic, low-level Hg exposure and body burden (ATSDR 1999; Faria 2003).

For instance, Kobal Grum *et al.* (2006) evaluated 53 former Hg miners and 53 controls using personality and mood questionnaires and found that the ex-miners tended to be more introverted and sincere, more depressive, more rigid in expressing their emotions, and more likely to have negative self-concepts than controls. According to the authors, regression results suggest that alcohol consumption per se and Hg exposure (measured as cumulative urinary Hg levels during employment) in interaction could explain the higher rates of depression among miners. The authors note that alcohol slows oxidation of elemental Hg (Hg^0) in the blood, which could cause more accumulation in the brain.

Similarly, Zachi *et al.* (2007) assessed the neuropsychological test performances and mood inventories of 26 patients who were diagnosed with chronic occupational mercurialism from exposure to Hg^0 several years prior, as compared to 20 controls. The patient group showed increased depression and anxiety symptoms ($p<0.001$). A statistically significant correlation was observed between mean urinary Hg levels and anxiety ($p<0.03$), even though mean urinary Hg levels were not elevated. Incidentally, the authors noted that 20 of the 26 patients were taking medication for the treatment of depression and/or anxiety.

3.6.2. Effects of low-level Hg exposure on mood – dental workers/ dentists and staff

Many studies of dental health personnel have found associations between mood and exposure to Hg at levels previously thought to be safe, using various measures of exposure, as described below. The studies generally excluded subjects with preexisting conditions that may have affected neurophysiological or neuropsychological testing (even though such conditions may have been caused by Hg). For instance, using a controversial X-ray fluorescence technique to measure tissue Hg levels in the heads of dentists, Shaprio *et al.* (1982) compared a

group of 26 dentists who had elevated head Hg levels to a control group of 17 dentists with no detectable head Hg, and found that the number of dentists with elevated scores on a general distress index was significantly greater in the high-Hg group.

Similarly, using the same X-ray fluorescence technique, Uzzell and Oler (1986) measured tissue Hg levels in the heads of female dental assistants. The authors compared 13 subjects who had elevated head Hg to 13 controls who had no detectable head Hg and found heightened general distress in the high-Hg group, particularly in the areas of obsessive compulsion, anxiety, and psychoticism.

In addition, using personal air monitors to estimate Hg exposure, Ngim *et al.* (1992) found a dose-dependent increase in aggression score, as well as many neurobehavioral deficits, in a study of 98 dentists and 54 controls. Furthermore, Gonzalez-Ramirez *et al.* (1995) measured urinary Hg after DMPS challenge for 15 dental health personnel and 13 controls and found a statistically significant adverse association between Hg levels and mood.

Likewise, Echeverria *et al.* (1995) compared 20 dentists who had high urinary Hg with 19 dentists who had no detectable levels and found significant urinary Hg dose-effects for poor mental concentration, emotional lability, somatosensory irritation, and total mood score, which included tension, fatigue, and confusion. Finally, in a later study, Echeverria *et al.* (1998) evaluated 49 dental health personnel and found statistically significant dose-effect relationships between urinary Hg and mood scores even though urinary Hg was not elevated (i.e., urinary Hg <4 μg/l). The authors also measured urinary Hg after a DMPS challenge, and found a significant association with disturbances in mood, motor function, and cognition. (The main findings of this study were the numerous statistically significant associations between urinary Hg levels and neurobehavioral deficits, which the authors found surprising given that the Hg levels were relatively low. Evidence from other studies also suggests that if Hg is retained in the tissues, urinary mercury levels may be counterintuitively low.)

3.6.3. Effects of Hg exposure from dental amalgam on mood – dental patients

Finally, one study on dental patients suggests Hg from amalgam as a possible etiological factor in mood disorders. In that study, Siblerud, Motl, and Kienholz (1994) compared mood inventories for 25 women with amalgams and 23 women without, and found that the women with amalgam fillings had higher scores for fatigue, insomnia, anger, depression, and anxiety. The women with amalgam fillings also had significantly higher levels of Hg in the oral cavity before and after chewing gum – in agreement with the experimental observations of Brune that have been referred to above (Brune 1985, 1986, 1988), showing that the toothbrush is an effective tool for enhancing the rate of amalgam corrosion.

3.6.4. Suicide

According to a 1977 review, in severe cases of chronic Hg poisoning, depression may reach suicidal proportions (Gerstner & Huff 1977). Subsequently, in a ten-year prospective cohort study, Arnetz *et al.* (1987) found an elevated standardized mortality ratio (SMR) for suicide in male dentists compared to other male academics.

More recently, in a post-mortem study mentioned earlier, Guzzi *et al.* (2006) measured Hg levels in the brain, thyroid, and kidney in 18 cadavers. The authors reported that among the eight suicide cases, five (63%) had more than 12 occlusal amalgam surfaces, while only one (10%) among the other 10 cadavers had as many amalgam fillings. The levels of Hg in the suicide cases were on average about three times higher than in the non-suicide cases at all three anatomic sites. Finally, in a study of occupational exposure of former Hg miners described earlier, Kobal Grum *et al.* (2006) reported that miners at the Idrija Hg mine in Slovenia have a historically high rate of suicide – 40 of 1589 miners (2.5%) in 1950–1995.

Indeed, suicide standard mortality rates have been found to be higher for dentists than for the population at large. However, the rates for other medical professionals are also elevated, perhaps related to the professionals' access to medications; no definitive conclusion can be drawn from the observed increased suicide rate in dentists (McComb 1997).

4. PLAUSIBILITY OF THE MECHANISMS BY WHICH HG INTOXICATION CAUSES ILLNESS

Mercury has no known biological function; it is solely a toxic element (Kade 2012; Farina *et al.* 2013). The most cytotoxic forms of Hg occur in its fully oxidized state, both in its cationic (Hg^{2+}) and organic forms that are found in the environment, foods and pharmaceuticals. These fully oxidized forms of Hg have a strong affinity for nucleophiles, particularly thiol (-SH) and selenol (-SeH) functional groups within proteins (Farina *et al.* 2013). Thiols, also known as sulfhydryls, include the amino acid cysteine, and the antioxidant glutathione (GSH). Thiols such as cysteine often serve as the active sites of enzymes, cofactors, receptors, cytokines, ion channels, transport proteins, and transcription factors (ATSDR 1999; Berlin *et al.* 2007). These biomolecules play critical roles in the fundamental cellular processes that are essential for life. By binding to these thiol components, Hg alters or blocks normal biochemical function, resulting in a plethora of interacting effects across many organ systems. Plausible early targets in Hg toxicity are ion channels, which affect membrane potential, cellular excitability, cell signaling, neurotransmitter release, and gene expression (Sirois & Atchison 1996).

Mercury's affinity for selenols is even stronger than for thiols; selenols form almost irreversible covalent

bonds with any oxidized form of Hg. Selenium (Se) has a lower natural geochemical abundance than any other known nutrient element. However, biologically important selenols include GSH peroxidase and thioredoxin reductase, which are discussed later.

Mercury also targets disulfide bonds, which provide much of the tertiary and quaternary structure for proteins. For example, the cys-loop family of ion channels employs a disulfide bond as the active site of its extracellular domain. By breaking this disulfide bond, Hg alters the structure and function of the ion channel, which thus alters mineral transport into the cell, resulting in mineral dyshomeostasis, disruption in the cell's ability to maintain proper ionic metal equilibrium (homeostasis) in response to changing environmental conditions.

These molecular mechanisms lead to the toxic effects described below, including increased oxidative stress, depletion of antioxidant defenses, alteration of essential mineral homeostasis, mitochondrial dysfunction, immune effects including alteration of gut flora, and dysregulation of hormones and neurotransmitters. These effects in turn are likely to cause issues of fatigue, inflammation, immunity, and mood.

4.1. Pro-oxidant effects

In the central nervous system, Hg species increase extracellular glutamate, an excitatory neurotransmitter, both by inhibiting glutamate uptake and by stimulating glutamate release into the synaptic cleft (Farina *et al.* 2013). Overactivation of the NMDA glutamate receptor leads to an increased influx of calcium ions (Ca^{2+}) due to the receptor's high permeability to this mineral. High intracellular calcium activates a number of enzymes that are associated with the generation of reactive species of oxygen and nitrogen, resulting in oxidative stress, altered membrane potentials, and mitochondrial dysfunction (Farina *et al.* 2013). Furthermore, overactivation of the NMDA glutamate receptor is associated with depression (Sowa-Kućma *et al.* 2013; Zarate *et al.* 2013) and suicide (Sowa-Kućma *et al.* 2013).

4.2. Effects on antioxidant defense

Glutathione is a key antioxidant and coenzyme in biological systems. The glutathione system includes reduced (GSH) and oxidized (GSSG) forms of glutathione; the enzymes required for its synthesis and recycling; and the enzymes required for its use in metabolism and in mechanisms of defense against free radical-induced oxidative damage. The glutathione molecule itself, as well as the active sites for several enzymes in the glutathione system, contain thiols (as cysteine) which are targets for Hg binding. By binding thiols in glutathione and its related enzymes, Hg species deplete the available level of this important molecule and also impair its synthesis, use, and recycling. The many functions of glutathione include detoxification, metabolic regulation, maintenance of neurotransmitters, protection of membranes, and modulation of signal transduction (Limón-Pacheco and Gonsebatt 2010). A common pathological hallmark in various diseases is the increase in oxidative stress and the failure of antioxidant systems, marked by a decrease in GSH (Limón-Pacheco & Gonsebatt 2010).

Thioredoxins are a class of antioxidant proteins that exert a range of regulatory activities by chemically reducing target molecules. Like the glutathione system, the thioredoxin system comprises the molecule itself and the enzymes required for its synthesis, use, and recycling. Thioredoxins contain two thiol active sites, which are targets for Hg. The enzyme that recycles thioredoxin, thioredoxin reductase, contains both a selenocysteine and a disulfide active site, which are targets for Hg (Branco *et al.* 2012a,b). Thus, Hg depletes thioredoxin and also impairs its recycling. The result is a shift in the cellular redox balance, toward oxidation, thus altering regulatory activities.

4.3. Effects on zinc and copper status / homeostasis

Metallothioneins are a class of cysteine-rich proteins whose function is not entirely clear but which appear to bind, store, and regulate metals including Cu and zinc (Zn). Mercury and similar metals induce apometallothionein, which bind/s Hg itself, thus protecting against toxicity, while displacing Cu and Zn species, disturbing their homeostasis (Bjørklund 2013; Clarkson 1987; Davis & Mertz 1987; Hambidge *et al.* 1986; Kostial 1986; Underwood 1977). This disturbance in the metabolism and storage of Cu and Zn may be an important contributory cause of Zn deficiency. At least 300 Zn-dependent enzymes are known to exist, and there are even more Zn-dependent transcription factors (Oteiza & Mackenzie 2005; Prasad 2012). Zinc deficiency may not only cause immunosuppression (Hambidge *et al.* 1986; Prasad 1995, 1997), which may play a role in CFS, but may also have harmful consequences for the brain.

Evidence suggests that Cu and/or Zn levels are abnormal in CFS, FM, depression, anxiety, and suicide. CFS and FM patients show a deficiency in serum Zn (Maes *et al.* 2006; Werbach 2000), and these disorders show improvement in clinical symptoms with Zn supplementation (Maes *et al.* 2008). Studies in both depression and anxiety show low serum Zn levels and high serum Cu levels (Chang *et al.* 2013; Islam *et al.* 2013; Narang *et al.* 1991; Tao *et al.* 2013; Sowa-Kućma *et al.* 2013; Swardfager *et al.* 2013a,b). In addition, low Zn and high Cu levels are associated with high symptom severity in depression (Russo 2011). Further, low Zn levels are found in patients who have attempted suicide (Gronek & Kolomaznik 1989). Table 2 provides examples of Hg's effects and the underlying mechanisms that might explain many symptoms in CFS, FM, depression, anxiety, and suicide.

4.5. Gut microbe effects

Normal gut flora is a modulator of behavior (Diaz Heijtz *et al.* 2011) and immunity (Hansen *et al.* 2012;

Tab. 2. Possible mercury-related mechanisms underlying the following symptoms.

Symptom	Consequences of Mercury Exposure	Reference
Chronic or periodic fatigue	Impaired mitochondrial function	Li *et al.* 2012
Depression	Depressed dopaminergic and serotonergic activity; Overactivation of the NMDA glutamate receptor	Tsai *et al.* 1995; Zhou *et al.* 1999 Farina *et al.* 2013
Pain or discomfort in muscles	Decreased DNA content and collagen accumulation rates in human synovial cells	Goldberg *et al.* 1983; Lindh *et al.* 2002
Abnormal fatigue after physical exertion	Impaired mitochondrial function	Li *et al.* 2012
Impairment of concentration	Loss of large-caliber, long-range axons needed for conscious processing	Dehaene & Changeux, 2011; Kern *et al.* 2012
Impaired sleep	Decreased pineal hormone melatonin levels	Kobal *et al.* 2004
Muscle discomfort in the whole body	Erethism (excessive sensitivity of a body part to stimuli) Impaired mineral transport	Tchounwou *et al.* 2003
GI disturbance	Decreased glutathione necessary for maintaining gastrointestinal integrity Altered gut flora	Sen, 1997; Alhamad *et al.* 2012
Frequent infections	Immune suppression Depletion of antioxidant defenses	Nyland *et al.* 2012
Aching lymph glands	Immune suppression and lymphoproliferation	Tchounwou *et al.* 2003; Nyland *et al.* 2012
Sore throat	Increased pharyngeal inflammation Depletion of antioxidant defenses	Alhamad *et al.* 2012
Headache	Brain edema	Eto, 2006
Impaired memory	Neurodegeneration of the thalamus which is paramount in recall and recollection	Kakita *et al.* 2000; Pergola *et al.* 2013
Suicide	Depressed dopaminergic and serotonergic activity Overactivation of NMDA receptor	Tsai *et al.* 1995; Zhou *et al.* 1999 Sowa-Kućma *et al.* 2013

Tlaskalová-Hogenová 2004). Evidence suggests that Hg vapor (Hg^0) exposure from dental amalgam can alter the intestinal flora so as to increase Hg-resistant bacterial species, which in turn also become resistant to antibiotics (Lorscheider *et al.* 1995b; Summers *et al.* 1993).

4.6. Effects on mitochondria and ATP

Mercury's pro-oxidant effects and its depletion of antioxidant defenses are most apparent in mitochondria (Farina *et al.* 2013). Mitochondrial components that are particularly vulnerable to free radical oxidative damage include enzymes, lipid membranes, and mitochondrial DNA (Pieczenik & Neustadt 2007). In addition, several mitochondrial enzymes and cofactors contain cysteine, a preferred target for Hg binding. Mitochondrial damage increases cellular energy requirements for repair, in a positive feedback loop that creates additional mitochondrial damage (Pieczenik & Neustadt 2007).

In addition, Hg's pro-oxidant effects, described above, increase intracellular calcium, which, in turn, increases reactive oxygen species and lipid peroxidation of mitochondrial membranes. Mitochondrial dysfunction, i.e., impaired production of the energy molecule, adenosine triphosphate (ATP), has effects throughout the body, particularly in energy-intensive organ systems including the heart, brain, and immune system.

Although not mitochondrial, another energy-depleting effect of Hg is its disabling of the thiol-containing enzyme, creatine kinase, which buffers intracellular ATP for energy storage.

4.7. Immunological effects and metal allergy

Mercury-containing compounds can profoundly affect the immune system at concentrations well below those that damage the central nervous system (Vas & Monestier 2008). Mercury species can cause immunosuppression, immunostimulation, immunomodulation, delayed-type hypersensitivity (type 4 allergy), and autoimmunity, via mechanisms that include altering the production of immune cytokines. These effects are influenced by genetic factors, including major histocompatibility complex genes that differ widely among individuals (Vas & Monestier 2008).

Studies indicate that immune responses to toxic metals including Hg may be a factor not only in the development of various autoimmune diseases (Siblerud & Kienholz 1994; Sterzl *et al.* 1999; Hybenova *et al.* 2010), but also in nonspecific symptoms such as chronic fatigue and myalgia (Stejskal *et al.* 1999, 2006; Stejskal *et al.* 2013). In addition, some studies suggest that amalgam removal may halt, reduce, or reverse autoimmune disease (Hybenova *et al.* 2010; Prochazkova *et al.* 2004);

although the lack of consistent findings may reflect the additional exposures incurred if amalgams are removed without adequate protections, as well as genetics and other factors involved in autoimmunity and illnesses.

In allergic reactions, a metal such as Hg may act as a hapten, forming a complex with one or more biological macromolecules, which together act as an antigen. Such immune reactions may occur at concentrations far below that required to damage the central nervous system or kidney (Vas & Monestier 2008).

4.8. Hg effects on the brain

Mercury has a plethora of negative affects in the brain (Eto 2006). According to a review by Kern *et al.* (2012) of the brain pathology from Hg intoxication, Hg exposure in the brain can cause: (1) microtubule degeneration, specifically large, long-range axon degeneration with subsequent abortive axonal sprouting (short, thin axons); (2) dentritic overgrowth; (3) neuroinflammation; (4) microglial/astrocytic activation; (5) brain immune response activation; (6) elevated glial fibrillary acidic protein; (7) oxidative stress and lipid peroxidation; (8) decreased reduced glutathione levels and elevated oxidized glutathione; (9) mitochondrial dysfunction; (10) disruption in calcium homeostasis and signaling; (11) inhibition of glutamic acid decarboxylase (GAD) activity; (12) disruption of GABAergic and glutamatergic homeostasis; (13) inhibition of IGF-1 and methionine synthase activity; (14) impairment in methylation; (15) vascular endothelial cell dysfunction and pathological changes of the blood vessels; (16) decreased cerebral/cerebellar blood flow; (17) increased amyloid precursor protein; (18) loss of granule and Purkinje neurons in the cerebellum; (19) increased pro-inflammatory cytokine levels in the brain (TNF-α, IFN-γ, IL-1beta, IL-8); and (20) aberrant nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). In addition, Hg has been found to increase in serotonergic neurons (Oda-Eto *et al.* 2013, 2011). With this plethora of negative effects on the brain, it is highly plausible that Hg intoxication could manifest as a variety of behavioral disorders, psychosocial issues, mood disturbances, and neurodegenerative diseases.

5. GENETIC SUSCEPTIBILITIES TO HG INTOXICATION

Evidence suggests that the effects of Hg depend not only on dose but also on genetic susceptibilities involving common polymorphisms of numerous genes. For instance, Ekstrand *et al.* (2010) studied two strains of mice and two generations of hybrid offspring all exposed to identical concentrations of Hg in drinking water. In the parent generation, the authors found significant differences in whole-body retention that varied by both strain and gender. The trait causing Hg retention was not dominantly inherited in the F1 hybrids. The F2 hybrids showed large inter-individual variation, suggesting that multiple genetic factors affect Hg retention. The authors note that the heterogeneous human population may therefore show a large variation in Hg toxicokinetics.

In addition, several human studies have provided evidence that Hg toxicity has a strong genetic component. For instance, Echeverria *et al.* (2005) examined a polymorphism in brain-derived neurotrophic factor (BDNF) in a study of 194 dentists and 233 dental assistants. The authors found statistically significant adverse associations between urinary Hg and nine neurobehavioral measures among dentists and eight neurobehavioral measures among dental assistants. The BDNF status was associated with four measures in dentists and three in dental assistants, in an additive manner with Hg exposure. The polymorphism frequency for dentists and dental assistants was 5% and 4% respectively for the homozygous variant, and 26% and 30% for the heterozygous variant.

The next year, Wojcik *et al.* (2006) considered the Apo-lipoprotein (Apo) E4 genotype in a study of 465 patients diagnosed with chronic Hg toxicity who had severe fatigue (32.3%), memory loss (88.8%), and depression (27.5%). The authors found a significant correlation (p=0.001) between chronic Hg toxicity (based on Hg symptom score) and the Apo E4 genotype (which, the authors note, is believed to convey a decreased ability to bind and transport Hg – and has been implicated in Alzheimer's disease). Removal of amalgam fillings, when combined with appropriate treatment, resulted in a significant improvement in overall symptom scores (p<0.001), with an average reduction to 45% of baseline, i.e., to levels reported by healthy subjects, after a treatment and follow-up period that ranged from 9 months to 10 years. According to the authors, 1–2% of the population has homozygous Apo E4, and approximately 20% have heterozygous Apo E3/4, both of which convey an impaired ability to eliminate Hg.

Next, Heyer *et al.* (2009) examined a polymorphism in the gene encoding the enzyme, catechol O-methyltransferase (COMT), in a study of 183 male dentists and 213 female dental assistants. The homozygous polymorphism was adversely associated with self-reported symptoms as well as mood-scores, in an additive manner with Hg exposure, in the dental assistants but not the dentists. The polymorphism frequency for the male dentists and the female dental assistants was 44% and 42% respectively for the heterozygous variant, and 29% for the homozygous variant in both groups.

Subsequently, Echeverria *et al.* (2010) examined a polymorphism in the serotonin transporter (5-HTT) gene in a study of 164 dentists and 101 dental assistants. The polymorphism was adversely associated with five neurobehavioral measures in dentists and 12 in dental assistants, in an additive manner with Hg exposure. Adverse mood scores were associated with the variant in both groups. The polymorphism frequency for den-

tists and dental assistants was 20% and 24% respectively for the homozygous variant, and 40% and 56% for the heterozygous variant.

Recently, in a series of re analyses of the Casa Pia children's amalgam trial, which was a randomized, controlled, clinical trial that has been a cornerstone for claims that amalgam is safe, Woods *et al.* (2012, 2013, 2014) demonstrated that several common genetic variants are associated with increased susceptibility to Hg toxicity in children – as measured by significant and consistent declines in neurobehavioral test scores across multiple domains. In the first study (n=330), Woods *et al.* (2012) examined CPOX4, a genetic variant of the heme synthesis enzyme, coproporphyrinogen oxidase (CPOX) and found numerous dose-response associations between Hg exposure (as measured by cumulative urinary Hg levels) and various neurobehavioral deficits, particularly attention deficit. Specifically, among boys but not girls, numerous significant interaction effects between Hg exposure and CPOX4 were observed spanning all 5 domains of neurobehavioral performance. The polymorphism frequency was 25% for the heterozygous variant of CPOX4 and 3% for the homozygous variant. In a subsequent study of the same 330 children, Woods *et al.* (2013) examined common genetic variants of two isoforms of metallothionein, a class of storage molecules that affect both essential and toxic metal storage. Among boys but not girls, numerous significant interaction effects were observed between Hg exposure and the variants of both isoforms, alone and combined, that were detrimentally associated with neurobehavioural function across multiple domains. In the third study of the same 330 children, Woods *et al.* (2014) examined common genetic variants of catechol-O-methyltransferase (COMT), an enzyme that affects catecholamine regulation. Among boys but not girls, numerous interactions were observed between Hg exposure and genetic variants of COMT, which were detrimentally associated with neurobehavioral function across multiple domains. In each of these studies (Woods *et al.* 2012, 2013, 2014), the authors conclude that their findings suggest that children with common genetic variants bear increased susceptibility to the adverse neurobehavioral effects of Hg.

As described earlier, Hg affects the glutathione system in a feedback loop of increased oxidative stress and decreased antioxidant defenses, thus, the many polymorphisms of glutathione-related genes are candidates for study, and several have been shown to alter Hg retention and antioxidant status. Barcelos *et al.* (2013) evaluated polymorphisms in two glutathione-related genes, glutamyl cysteine ligase (GCL) and glutathione S-transferase (GST) in an Amazonian population (n=400) exposed to methyl-Hg in fish. The authors found that certain polymorphisms of both GCL and GST modified Hg concentrations in blood and hair, and a polymorphism of GST modified catalase activity.

Custodio *et al.* (2004) evaluated polymorphisms for GCL and GST in a Swedish population exposed to methyl-Hg in fish. The authors found that a polymorphism for each gene was associated with modified erythrocyte Hg levels. The frequencies for these two polymorphisms were 13% and 16%. The following year, Custodio *et al.* (2005) evaluated genotypes for GCL and GST, in a study of 309 gold miners, gold refiners and controls. The authors found that a GCL polymorphism was associated with higher Hg levels in blood, plasma, and urine. This polymorphism leads to decreased glutathione production, which would lead to less conjugation and biliary excretion of Hg, which could cause higher Hg levels in blood and urine. The polymorphism frequency was 41% for the heterozygous variant and 10% for the homozygous variant.

These genes may be the tip of the iceberg. Because Hg blocks thiol functional groups within proteins, and because these numerous proteins are coded by genes that vary among individuals, many such susceptibility genes are likely to exist (Berlin *et al.* 2007).

6. MERCURY EXPOSURE FROM DENTAL AMALGAMS AND CELL PHONES

Some studies suggest that there is additional concern with dental amalgams and the use of cell phones (Mortazavi *et al.* 2008). For example, Mortazavi *et al.* (2008) found that magnetic resonance imaging (MRI) and microwave radiation emitted from mobile phones significantly increased mercury release from dental amalgam restorations. They stated that exposure to 0.23 T MRI significantly increased the mean ± SD salivary mercury level from 8.6±3.0 mg/L before MRI to 11.3±5.3 mg/L 15 min after the imaging, in 30 people with dental amalgam restorations.

In a follow-up study, Mortazavi *et al.* (2014) assessed the effect of high-field MRI on Hg release from dental amalgam fillings. Healthy students (n=16) with identical dental decay, underwent similar restorative dentistry procedures and were randomly divided into two groups of MRI-exposed and controls. The difference between urinary Hg levels in the exposed and control group, 72 hrs after MRI (96 h after restoration), was found to be significantly higher in the MRI group.

7. CONCLUSION

Mercury's toxic effects are broad, variable, and idiosyncratic, and can often be delayed. The effects of chronic, low-dose exposures as from dental amalgam, as well as the modifying effects of genetic susceptibilities, are only beginning to be recognized. Mercury toxicity may be a continuum, with no safe threshold for exposure (World Health Organization 2005).

Mercury's molecular mechanism of toxicity – the binding of thiols and selenols – is unusually broad, resulting in altered structure and function of enzymes,

cofactors, receptors, cytokines, ion channels, transport proteins, and transcription factors. These mechanisms in turn increase oxidative stress, decrease antioxidant defenses, and alter redox balance, which then affect other biochemical processes, often in an interactive manner. Thus, it is understandable why, for example, the Hg-related inhibition of the biosynthesis of neurotransmitters such as serotonin, dopamine, noradrenaline, and GABA, may lead to depression, anxiety and other disorders.

But more research is needed to obtain an integrated understanding of diseases that appear to have multiple causal factors, such as CFS and FM. For example, some of the same biochemical mechanisms found in depression and anxiety might also be important in CFS and FM – with depression and anxiety being primarily brain diseases, while CFS and FM are systemic diseases predominantly affecting other organs and cell types.

This review reports the evidence that supports a link between amalgams and chronic illness, fatigue, depression, anxiety, and suicide; however, it should be mentioned that there are studies that do not support this hypothesis (Dixon 1998; Taut 2013; Bates 2006). For example, Bates (2006) conducted a comprehensive review of the epidemiologic evidence for the safety of amalgams and stated that studies show little evidence of effects on general chronic disease incidence or mortality, including chronic fatigue syndrome. However, Bates also concluded that few relevant epidemiologic studies are available and that better designed studies are needed.

The evidence provided in this review suggests that dental amalgams may be a significant contributing factor in the burden of disease. Furthermore, interactions between Hg and other causes of disease might be more the rule than the exception. However, it may be difficult to assess the relative importance of various causal factors in diseases of multifactorial etiology.

This review offers some preliminary mechanistic explanations for several clinical observations in Hg poisoning, especially the often observed neurological and psychiatric symptoms. However, full mechanistic explanations may be elusive for diseases that affect multiple cell types and organ systems in an interactive manner, as appears to be the case for CFS and FM.

This review has presented evidence suggesting a causal relationship between Hg exposure from dental amalgams and CFS, FM, depression, and anxiety. These disorders appear to share common mechanisms, thus are suggestive of a larger disorder – adult dental amalgam (ADA) syndrome – although multiple causes are likely. However, given the evidence, especially the frequent relief of symptoms with amalgam removal, consideration of Hg toxicity may be central to the effective clinical investigation and evaluation of many chronic illnesses, particularly those involving depression and fatigue.

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