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Comments on the Article "The Toxicology of Mercury and Its Chemical Compounds" by Clarkson and Magos (2006)

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Clarkson and Magos (2006) provide their perspectives on the toxicology of mercury vapor and dental amalgam. As scientists who are involved in preparing a German federal guidline regarding dental amalgam, we welcome additional scientific data on this issue. However, Clarkson and Magos do not present all the relevant studies in their review. The additional data provided here show that: (a) Dental amalgam is the main source of human total mercury body burden, because individuals with amalgam have 2–12 times more mercury in their body tissues compared to individuals without amalgam; (b) there is not necessarily a correlation between mercury levels in blood, urine, or hair and in body tissues, and none of the parameters correlate with severity of symptoms; (c) the half-life of mercury deposits in brain and bone tissues could last from several years to decades, and thus mercury accumulates over time of exposure; (d) mercury, in particular mercury vapor, is known to be the most toxic nonradioactive element, and is toxic even in very low doses, and (e) some studies which conclude that amalgam fillings are safe for human beings have important methodogical flaws. Therefore, they have no value for assessing the safety of amalgam.

Keywords Amalgam, Autism, Ethylmercury, Mercury, Toxicity, Thimerosal

INTRODUCTION

In their, 2006 article, Clarkson and Magos (2006) provide their perspectives on the toxicology of mercury vapor and dental amalgam. In the following comments, we challenge some of the conclusions of Clarkson and Magos on the basis of new scientific literature.

SIGNIFICANCE OF DENTAL AMALGAM FOR MERCURY BODY BURDEN

Dental amalgam is the main source of mercury body burden, as studies in animals (Danscher et al., 1990; Galic et al., 1999, 2001, Hahn et al., 1989, 1990; Lorscheider et al., 1995; Lorscheider and Vimy, 1991; Vimy et al., 1990) and humans show. An approximate 2–5-fold increase of the mercury level in blood und urine as well as a 2- to 12-fold increase of the mercury concentration in several body tissues was observed in amalgam bearers (Barregard et al., 1999; Becker et al., 2002, 2003; Drasch et al., 1992, 1994, 1997; Egglestone and Nylander, 1987; Gottwald et al., 2001; Guzzi et al., 2002, 2006; Levey et al., 2004; Lorscheider et al., 1995; Kingmann et al., 1998; Mortada et al., 2002; Nylander, 1986, 1991; Nylander et al., 1987; Pizzichini et al., 2003, Weiner and Nylander, 1993; Zimmer et al., 2002). Also, mercury from maternal amalgam fillings leads to a significant increase of mercury concentration in the tissues and the hair of fetuses and newborn children. Placental, fetal, and infant mercury body burden correlates with the numbers of amalgam fillings of the mothers (Ask et al., 2002 ; Drasch et al., 1994 ;, Holmes et al., 2003 ; Morgan et al., 2002; Takahashi et al., 2001, 2003; Vather et al., 2000; Yoshida et al., 2002, 2004). Mercury levels in amniotic fluid (Luglie et al., 2003) and breast milk (Drasch et al., 1998; Oskarsson et al., 1996; Vimy et al., 1997) are significantly correlated with the number of maternal amalgam fillings. Mercury from amalgam may be transformed into organic mercury compounds by microorganisms in the gastrointestinal tract (Leistevuo et al., 2001; Heintze et al., 1983; Yannai et al., 1991). Leistevuo et al. (2001) found an increase of methylmercury concentration in amalgam bearers of three times compared to persons without amalgam, although frequency and kind of fish consumption were identical in both groups.

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TOXICITY OF MERCURY

Mercury is asssumed to be the most toxic nonradioactive element. This extraordinary toxicity is determined by the following properties:

1. It is the only metal representing at room temperature a volatile gas, which is is readily absorbed (80%) by the respiratory system.
2. Mercury vapors penetrate biological tissues with great ease, because of its monopolar atomic configuration.
3. Once inside the cells, mercury vapor is oxidized to Hg^{2+}, the toxic form of mercury, which binds covalently to thiol groups of proteins inhibiting their biological activity.
4. Hg^{2+} is more toxic than Pb^{2+}, Cd^{2+}, and other metals because it has an extremely high affinity due to "covalent bond" formation with thiol groups (cysteines in proteins), causing irreversible inhibition (binding constant 10^{30-40}). Other metals form reversible bonds with proteins and are therefore less toxic. This might explain the exceptionally long half-life of mercury in non-renewing tissue (e.g., brain), from several years to decades (Hargreaves et al., 1988; Opitz et al., 1996; Sugita, 1978).
5. Hg^{2+} does not bind tightly enough to the carboxylate groups of natural organic acids (natural chelators like citrate) to prevent its toxicity.
6. Chelating agents, like ethylenediamine tetraacetic aced (EDTA), which normally inhibit the toxic effect of heavy metals, have no inhibitory effect on the toxicity of mercury or may even increase it (Duhr et al., 1993; Pendergrass and Haley, 1996). Other chelating agents (DMPS and DMSA) inhibit the toxic effect of Cd^{2+} and $Pb^{2+,}$ but not of Hg^{2+} (Soares et al., 2003). DMPS, DMSA, or natural chelators like vitamin C, glutathione, or alpha-lipoic acid are not able to remove mercury from nervous-system tissues. (Aposhian et al., 2003). DMPS or DMSA may even increase the inhibitory activity of Hg^{2+} and Cd^{2+}on enzymes but not that of Pb^{2+} (Nogueira et al., 2003).

Furthermore, DMPS in animals led to an increase of Hg concentrations in spinal cord (Ewan and Pamphlett, 1996). Mercury has been shown to be 10 times more toxic than lead in vivo (Thier et al., 2003; Stoiber et al., 2004a, 2004b).

NO CORRELATION BETWEEN URINARY MERCURY LEVELS AND CRITICAL ORGANS

Clarkson and Magos (2006) state on page 618: "Urinary mercury may also be a rough indicator of the total body burden of mercury."

Contrary to this statement, the World health Organization (WHO) writes:

> There are at present no suitable indicator media that will reflect concentrations of inorganic mercury in the critical organs, the brain or kidney. . . . One important consequence is that concentrations of mercury in urine or blood may be low quite soon after exposure has ceased, despite the fact that concentrations in the critical organs may still be high. (WHO, 1991, p. 61)

This is further confirmed in a more recent publication by the WHO (2005).

There is rising evidence that mercury concentrations in blood and urine do not adequately represent the mercury levels in body tissues. It hase been shown in experiments with animals and humans that in spite of normal or low mercury levels in blood, hair, and urine, high mercury levels are found in critical tissues like brain and kidney (Danscher et al., 1990; Drasch, 1997; Hahn et al., 1989, 1990; Hargeaves et al., 1988; Holmes et al., 2003; Lorscheider et al., 1995; Opitz et al., 1996; Vimy et al., 1990; Weiner and Nylander, 1993).

Furthermore, Drasch et al. (2001, 2002, 2004) showed that 64% of individuals who were occupationally exposed to mercury vapor and have the clinical diagnosis of mercury intoxication had urine levels of mercury below 5 μg/L, which represent the no-observed-adverse-effect level (NOAEL). The same results were found for mercury levels in blood and hair (Drasch et al., 2001, 2002, 2004).

Paradoxical Association Between Mercury Levels in Urine and Body Tissues?

Deceased subjects who showed only 0.3 ng mercury/ml urine had up to 350 ng mercury/g kidney tissue (wet weight) in kidney specimens. On the other hand, subjects with high urine levels of mercury (above 2 ng/ml) had only 150 ng mercury/g in their kidney tissues. (Drasch et al., 1997).

Furthermore, especially the subjects with highest urine levels of mercury (after challenge with DMPS) showed the best recovery rates from neuropsychological complaints after removal of their amalgam fillings (Stenman and Grans, 1997). Also, children with highest mercury levels in hair showed better performance in developmental tests (Grandjean et al., 1995).

Another study indicates that autistic children had up to 15 times lower mercury levels in their infant hair than healthy controls, despite higher exposure to mercury in the womb through maternal dental amalgams and Rho-gamma-D-injections, wich contain mercury as a preservative, during pregnancy. Furthermore, the lower the mercury levels in infant hair, the higher was the severity of autism (Holmes et al., 2003).

In the study of Zimmer et al. (2002), individuals with dental amalgam, who reported amalgam-derived complaints showed a tendency to have lower mercury levels than individuals with dental amalgam but without complaints (Walach et al., 2003).

It is important to understand that given the same exposure to mercury, individuals with high levels of mercury in urine or hair may have a better excretion capacity for mercury. Presumably, this leads to a lower mercury body burden or to fewer mercury-derived complaints compared to individuals with low levels of mercury in urine or hair (Muhlendahl, 2005; Mutter et al., 2005).

Therefore, risk assesments or reviews regarding the safety of dental amalgam, like that of Clarkson and Magos (2006), the

Food and Drug Administration (FDA) (Anonymous, 2006), and Life Science Reserach Office (LSRO) (Brownawell et al., 2005) using mercury-levels in urine as the gold standard for the assessment of clinical symptoms or the estimation of mercury levels in critical tissues might lead to completely distorted conclusions.

For lead, health problems arise at blood levels far below the presently accepted safety limits (Menke et al., 2006; Bellinger and Needleman, 2003; Rogan and Ware, 2003; Canfield et al., 2003; Lin et al., 2003; Glenn et al., 2003). The same may be assumed for the more toxic mercury.

Body Half-Time Period of Mercury

Clarkson and Magos (2006) state in their review (p. 617) that the "whole body half-time (of mercury) [was] about 58 days."

Particularly in the brain, mercury could exhibit much longer half-time periods. There is, for example, the case of a healthy worker who was accidently exposed to mercury vapor. Four weeks afterward, mercury levels in urine decreased to normal levels due to chelation therapy with D-penicillamine. After the accident, the worker suffered for 16 years from severe fatigue, irritability, burning stomach, and diabetes, which were diagnosed as "organic psycho syndrome" not caused by his mercury exposure because mercury levels in urine were found to be normal. He was never able to go to work again. At 16 years after mercury exposure he died of lung cancer. Autopsy revealed elevated mercury levels in his cerebellum (2190 ng Hg/g), occipital lobe (1090 ng Hg/g), thalamus (1010 ng Hg/g), kidneys (1650 ng Hg/g), lungs (600 ng Hg/g), and thyroid glands (250 ng Hg/g) (Opitz et al., 1996). Interestingly, most of the mercury was found to be intracellularly near to cell nuclei. Mercury was also acummulated in motoneurons and the basal ganglia.

During 16 years after mercury exposure, these extraordinary high mercury levels in the body tissues were not excreted, neither naturally nor through frequently applied chelation therapy. According to Clarkson and Magos (2006) with their postulated "whole body half-time of about 58 days," 99% of the mercury body load should be excreted after even 1 year of mercury exposure; 16 years after exposure, no mercury should be detectable in the tissues.

Other authors also report about the extremly long half-time or long-lasting effect of mercury in body tissues (Hargreaves, 1988; Takahata, 1970; Sugita, 1978; Kishi, 1994; He, 1984; Kobal et al., 2004; Letz et al., 2000).

Adverse Health Effects Through Dental Amalgam?

Clarkson and Magos (2006) write on page 612: "However, other than rare cases of contact allergy, no convincing evidence is yet forthcoming that dental amalgam can cause adverse health effects."

In our view this statment is somewhat weakly founded, as there are data not cited by Clarkson and Magos that show that dental amalgam may cause adverse health effects. We would like to provide some of the evidence missing in their review.

1. Skin Allergies, Lichen

There is a correlation between atopic eczema and immunoglobulin (Ig) E levels and the body burden of mercury (Weidinger et al., 2004). Amalgam fillings can induce lichenoid reactions (Berlin, 2003; Dunsche et al., 2003a, 2003b; Martin et al., 2003; Wong & Freeman, 2003). In more than 90% of the cases, these lesions have been found to recover by removal of amalgam, no matter whether an allergy patch test was positive or not. Granulomatosis improved likewise (Guttman-Yassky et al., 2003).

2. Autoimmune Disorders and Sensitivity

Constant low-dose mercury exposure, as is common with amalgam bearers, has been considered as a cause for certain autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, or systemic lupus erythematosis (SLE), by many authors (Bartova et al., 2003; Berlin, 2003; Hultmann et al., 1994, 1998; Pollard et al., 2001; Prochazkova et al., 2004; Stejskal and Stejskal, 1999; Stejskal et al., 1999; Sterzl et al., 1999; Via et al., 2003; Sterzl et al., 2006). These effects can occur with exposure below acceptable safety limits (Kazantzis, 2002). According to a Swedish risk analysis the frequency of particularly sensitive persons is considered to be 1% (Berlin, 2003). The Commission of Human Biomonitoring of the German Federal Environmental Agency (Umweltbundesamt) estimates that approximately 1–4% of the population can have reactions due to being particularly sensitive to amalgam (Kommission Human-Biomonitoring des Umweltbundesamtes, 1999). This rate of 1–4% was confirmed by studies that rated immunological disorders caused by amalgam at 1–3% of the population (Marcusson, 1999). This represents a significant medical and economical problem when considering the present existence of amalgam fillings in a large percentage of the population. A commissioner who had been appointed to provide data on amalgam from the Canadian Federal Health Board had even estimated that up to 25% of individuals with amalgam have amalgam-derived complaints (Richardson, 1995).

3. Kidneys

In animal experiments an impairment of renal functions due to amalgam fillings has been reported (Boyd et al., 1991; Galic et al., 2001; Pollard et al., 2001). Humans with amalgam fillings show more signs of tubular and glomerular damage when compared to individuals without dental amalgams (Mortada et al., 2002).

4. Genotoxicity and Oxidative Stress

Aberrations of chromosomes can be provoked through amalgam in cell cultures (Akiyama et al., 2001) (Schmid et al., 2007). Amalgam bearers show significantly increased oxidative stress in saliva (Pizzichini et al., 2000, 2002) and blood (Pizzichini et al., 2001, 2003), which correlates with the numbers of fillings. Low mercury concentrations lead to increased oxidative

stress und reduction of the glutathione concentration in vitro (Olivieri et al., 2000, 2002). Mercury deposited in the tissue is mostly bound to selenium, which means that this selenium is no longer available for the body. Mercury from amalgam may aggravate a latent deficiency of selenium, particularly in countries with suboptimal selenium supply (e.g., in Central Europe) (Drasch et al., 2000).

5. Alzheimer's Disease (AD)

Clarkson and Magos (2006) question the hypothesis that mercury may contribute to the development of Alzheimer's disease (AD). Although our overview was cited by Clarkson and Magos (2006), we would like to summarize briefly the statements made in this review in order to clarify our view (Mutter et al., 2004a).

1. No metal other than mercury is capable to produce every single change in the nervous system of animals and in cell tests that is typical for AD, including the increase of ß-amyloid and the formation of neurofibrillar tangles (NFT).
2. If aluminum or other metals are present in the body together with mercury it is highly likely that synergistic toxic effects occur.
3. Some studies found elevated mercury levels in brain tissues or body fluids of individuals with AD.
4. The development of AD takes up to 30–50 years (Braak et al., 1997).
5. Since about 95% of all AD cases are triggered by exogenic factors and the disease is now pandemic in developed countries, the main exogenic factor should be present since about 50 years in many people, both in rural and in urban sites. This matches with the rising use of dental amalgam after World War II 50 years ago.
6. The risk of AD increases with the incidence of dental decay.
7. It is known that the presence of the apolipoprotein E subtype (Apo-E-4 allele) is a major risk factor for developing AD (Farrer et al., 1997; Ritchie and Dupuy, 1999). Exactly why Apo-E-4 is a major risk factor for AD is yet not known. A possible link could be the fact that Apo-E-4 has reduced the detoxifying abilities compared with the other two subtypes (Apo-E-2, Apo-E-3). Apo-E-4 has no thiol groups, unlike to the other forms, which may have the ability to bind and detoxify heavy metals like mercury (Godfrey et al., 2003; Pendergrass & Haley, 1996) and lead (Stewart et al., 2002).

In our view these arguments show that mercury plays a major factor in the development of AD and is even more important than aluminum.

The average mercury load in the brain of AD patients was 20 to 178 ng Hg/g; in some cases the load exceeds up to (236–698 ng Hg/g). In 15% of brain samples the mercury load was above 100 ng Hg/g (Ehmann et al., 1986; Thompson et al., 1988; Saxe et al., 1999). The average mercury load in the pituitary gland was as high as 400 ± 100 ng Hg/g (Cornett et al., 1998).

Considering that the mercury load decreased due to the death of neurons during the progress of the disease, the total load must have been even greater at the beginning of the pathological changes in brain, which precede clinical diagnosis of AD by up to 50 years (Braak et al., 1997).

The typical hallmarks in brain tissues occurring during AD have been produced by far lower concentrations of inorganic or elemental mercury in experimental settings. Mercury concentrations of 0.02 ng Hg/g (2 μl 0.1 μM Hg in 2 ml substrate) led to the total destruction of tubuli and to the degeneration of axons, which in turn led to the formation of neurofibrillary tangles (NFT) (Leong et al., 2001). In other experiments a mercury concentration of 36 ng Hg/g (0.18 μM Hg) led to the excretion of ß-amyloid 40 und 42, to an increase of oxidative stress, and to hyperphospholyration of Tau as a prerequesite for the formation of NFT (Olivieri et al., 2000, 2002).

Transferring these results to the human brain, it is sensible to assume similar changes, particularly as the average concentration in the brain tissues of some humans exceeded the mercury concentrations in these experiments by far.

Some scientists argue that results gained by animal or cell testing are not comparable to the situation of the human body. However, as humans are exposed to many other pathogenetic sources, we think that the effects add up or are even synergistic (Schubert et al., 1978; Haley, 2002). Moreover, animals like rats are capable of producing the antioxidant vitamin C by themselves when exposed to stress.

Methodical Flaws in Studies Cited by Clarkson and Magos (2006)

For studying toxic effects it is necessary to compare at least two samples: one that was exposed to the substance in question and one that was not. One of the main problems in most of the amalgam studies is that the vast majority did not incorporate a true control group that was never exposed to dental amalgam. Even when comparing samples with and without dental fillings, the sample without the dental fillings probably was exposed to dental amalgam earlier in life.

The studies cited by Clarkson and Magos (2006) as a proof of the putative harmlessness of amalgam do not use "proper" non-amalgam control groups. We would like to describe a prominent example:

The Swedish twin study (Björkmann et al., 1996) actually only compared 57 twin pairs in a co-twin analysis, and not 587 as mentioned by Clarkson and Magos (2006). As the average age of the sample was 66 years, 25% had no teeth at the time of investigation, many had missing teeth, and an unknown number had crowns using other dental materials. Root fillings with amalgam and amalgam fillings under crowns were not calculated. As an allegedly "non-amalgam" group, they were compared with individuals who still had dental amalgam fillings. The authors found that individuals with more amalgam fillings (which means also more own teeth) had a better health status. It is fair to assume that individuals with few or no teeth or teeth that have been restored with dental materials other than amalgam had probably had dental amalgam previously. As Hg accumulates in organs,

this "amalgam-free group" might have been equally or even have been more exposed to mercury than the "amalgam group" with currently existing amalgam fillings.

Impairment of Cognitive Functions and Occupational Exposure to Amalgam

Dentists working with amalgam have an increased Hg exposure (Harakeh et al., 2003; Tezel et al., 2001; Nylander and Weiner, 1991). Mercury exposure from amalgam that is considered to be below the safety limit resulted in measurable changes in cognitive or neurobehavioral functions (Bittner et al., 1998; Echeverria et al., 1995, 1998; Siblerud, 1989, 1992; Siblerud et al., 1993, 1994; Heyer et al., 2004; Echeverria et al., 2005, 2006). Low-level exposure to mercury vapor has been shown to lead to behavioral changes in adult mice (Yoshida et al., 2004) and to the impairment of color discrimination in humans (Urban et al., 2003).

Studies on dental staff workers show increased neuropsychological complaints (Aydin et al., 2003; Bittner et al., 1998; Echeverria et al., 2005, 2006; Heyer et al., 2006; Ngim et al., 1992; Ritchie et al., 2002) or pathological muscle biopsies (Nadorfy-Lopez et al., 2000). Visual evoked potentials in Hg-exposed staff (among them dentists) show significant changes when compared to controls (Urban et al., 1999). A meta-analysis showed neuropsychological impairment in 686 persons exposed occupationaly to mercury vapor compared to 579 controls (Meyer-Baron et al., 2002). Mercury levels in urine of these samples may be easily reached by exposure to amalgams (Lorscheider et al., 1995).

Infertility

The prevalence of infertility has increased from 8 to 15% in the last two decades. Women with a higher number of amalgam fillings or an increased excretion of mercury in the urine (after DMPS) suffered more frequently from infertility than controls (Gerhard et al., 1998a, 1998b; Gerhard and Runnebaum, 1992). Female dental assistants, who were exposed to amalgam, had a higher rate of infertility (Rowland et al., 1994). Heavy-metal detoxification led to spontaneous pregnancies in a considerable part of the infertile patients (Gerhard et al., 1998b). Exposure to mercury may also lead to decreased male fertility (Sheiner et al., 2003), although low-level mercury exposure does not necessarily cause infertility but appears to have a negative impact on fertility (Podzimek et al., 2003, 2005). The Norwegian study that is often cited as a proof for mercury exposure in dental clinics not causing infertility suffers from methodological flaws insofar as only including women who had already borne at least one child. Women without children were excluded. Such a study certainly cannot answer the question of whether working with amalgam leads to infertility or not. Moreover, the exposure time to amalgam was not calculated and thus not included as a covariate into the study.

Multiple Sclerosis (MS)

The prevalence of multiple sclerosis (MS) has been shown to be correlated with the prevalence of caries (Craelius, 1978; McGrotheret al., 1999) and the prevalence of amalgam (Baasch, 1968; Ingalls, 1983). Several MS epidemics occurred after acute exposure to mercury vapor or lead (Ingalls, 1986). In animal models, inorganic mercury caused a loss of Schwann cells, which build the myelin sheaths and stabilize the axons of neurons (Issa et al., 2003). Autoimmune pathogenesis, including antibodies against myelin basic protein (MBP), can be provoked by mercury and by other heavy metals (Stejskal and Stejskal, 1999). Also, a 7.5-fold increased concentration of mercury could be found in the cerebrospinal fluid (CSF) of MS patients (Ahlrot-Westerlund, 1989). It would be difficult to speculate that the presence of this increase in the CSF would not at least exacerbate the problems associated with MS or any neurological disease.

MS patients who had their amalgam fillings removed showed fewer depressions and less hostile aggressions and psychotic and compulsory behaviors when compared to a group of MS patients with amalgam fillings (Siblerud, 1992). They also had significantly lower blood mercury values (Siblerud and Kienholz, 1994). After the removal of the amalgam fillings in MS patients the oligoclonal bands in the CSF disappeared (Huggins et al., 1998). Removal of dental amalgam led to recovery in a significant proportion of MS patients (Prochazkowa et al., 2004). A retrospective study on 20,000 military individuals revealed a slightly but significantly higher risk for MS in individuals with more amalgam fillings (Bates et al., 2004). This risk may even be underestimated, because the study cohort consisted primary of healthy persons at the time of entrance to military, which was selected by the process of military scrutiny (Bates et al., 2004). The OR for MS was 3, 9 compared to individuals without amalgam (Bates et al., 2006). Another problem in some studies regarding this topic is that the dental status before or at the time of the onset of multiple sclerosis was not documented.

Amyotrophic Lateral Sclerosis (ALS)

Mercury vapor is absorbed by motor neurons (Pamphlett and Coote, 1998), where it leads to increased oxidative stress. Mercury vapor is also suggested to promote motor neuron diseases like amyotrophic lateral sclerosis (ALS) (Pamphlett et al., 1998, Pamphlett and Waley, 1996; Stankovic, 2006). It is proposed that mercury enhances glutamate toxicity in neurons, which is one factor in ALS (Albrecht and Matyja, 1996). Case reports show a correlation between accidental mercury exposure and ALS (Adams et al., 1983; Schwarz et al., 1996). There is a reported case of a Swedish woman with more than 34 amalgam fillings who suffered from ALS. After removal of these fillings and treatment with selenium and vitamin E she completely recovered (Rehde and Pleva, 1994). A retrospective study reported a statistically significant association between increased amalgam fillings and the risk of motoneuron diseases (Bates et al., 2004).

Frequently Reported Symptoms and Markers of Sensitivity

Among the symptoms most frequently reported due to amalgam fillings in amalgam-sensitive subjects are chronic fatigue, headache, migraine, increased susceptibility to infections, muscle pain, lack of concentration, digestion disorders, sleeping disorders, low memory capacity, joint pain, depression, heart sensations, vegetative dysregulation, mood disorders, and many more (Engel, 1998; Godfrey et al., 2003; Lindh et al., 2002; Siblerud, 1989, 1992; Siblerud et al., 1993, 1994; Wojcik et al., 2006).

Until recently, it was not possible to differentiate between "amalgam-sensitive" and "amalgam-resistant" persons by their biomarkers or an epicutaneous test (patch test) (Gottwald et al., 2001; Zimmer et al., 2002). Surprisingly, it could be shown that subjects could react to a mercury patch test with psychosomatic symptoms although there was no allergic reaction of the skin (Marcusson, 1996).

In addition, neutrophil granulocytes in amalgam-sensitive subjects react differently compared to those in amalgam-resistant subjects (Marcusson and Jarstrand, 1998), and different activities of the superoxide dismutase could be found (Marcusson et al., 2000).

It could also be shown that amalgam-sensitive persons are significantly more likely to be carriers of the apolipoprotein E4 allele (APO-E4) than symptom-free controls and are less likely to carry the APO-E2 (Godfrey et al., 2003, Wojcik et al., 2006). APO-E4 is known to be a major risk factor for AD, whereas APO-E2 decreases the risk. It has been postulated that this is caused through the difference in capacity to remove heavy metals from the CSF (Wojcek et al., 2006; Godfrey et al., 2003; Haley, 2002; Mutter et al., 2004a, Pendergrass and Haley, 1996; Stewart et al., 2002).

Amalgam-sensitive persons more often show signs of sensitivity to mercury and nickel in a special, validated lymphocyte transformation test (MELISA) (Prochazkova et al., 2004; Sterzl et al., 1999; Stejskal et al., 1996, 1999; Valentine-Thon et al., 2003, 2006).

Improvement After Removal of Amalgam

Clear improvement of health or recovery of the already mentioned diseases (including multiple sclerosis and other autoimmune diseases) has been reported after amalgam removal, and also in studies with high case numbers (in most of the cases with elaborate protective measures to minimize mercury exposure) (Kidd, 2000; Lindh et al., 2002; Engel, 1998; Huggins et al., 1998; Prochazkova et al., 2004; Siblerud and Kienholz, 1994; Stejskal et al., 1999; Sterzl et al., 1999, 2006; Stromberg and Langworth, 1998; Valentine-Thon et al., 2006; Wojcik et al., 2006).

Autism and Mercury?

Clarkson and Magos (2006) question that vaccines containing mercury and maternal amalgam fillings play a role in the development of autism. According to our view (Mutter et al., 2005a), the critique by (Muhlendahl, 2005), and our response (Mutter et al., 2005b), the following crucial arguments are to be made:

1. Experimental as well as epidemiological studies indicate that mercury exposure could be responsible for autism or deterioration of the disease. Prenatal and postnatal sources (maternal amalgam, vaccines of the mother, mercury from preservatives and from vaccines of the child) together with a geneticly founded sensitivity may trigger autism.
2. In animal experiments, vaccination led to autistic symptoms (Hornig et al., 2004).
3. The levels of mercury in urine of autistic children is increased by three- to fivefold after appropriate chelation with DMSA compared to healthy children (Bradstreet et al., 2003). Autistic children also excrete higher concentrations of coproporphyrine (Geier and Geier, 2006; Nataf et al., 2006). This was also seen in dentists (Echeverria et al., 2005, 2006; Heyer et al., 2006). Chelation therapy (DMSA) normalized the abnormal coproporphyrin levels in autistic children (Geier and Geier, 2006; Nataf et al., 2006). The increased level of coproporphyrin in autistic children could only be explained by mercury exposure.
4. Epidemiologic data suggest a correlation of mercury exposure through environmental pollution and the risk of developing autism (Palmer et al., 2006).
5. Autistic children show decreased levels of the natural chelator glutathione (James et al., 2004), and mercury is able to cause this phenomenon (James et al., 2005).
6. In some therapy studies chelation therapy led to the improvement of symptoms in up to 60–80% of the cases. The Autism Research Institute therefore lists chelation as the most effective therapeutic approach among 88 therapies including 53 medications (Autism Research Institute, 2005).
7. Autistic children show elevated mercury levels in baby teeth, which represents levels in brain (Adams et al., 2007).

Mercury in Newborns and Infants

The study cited by Clarkson and Magos to prove the safety of Thimerosal was conducted by Pichichero, who may have a conflict of interest. Blood mercury levels were measured in 33 babies after days and weeks after vaccination (Pichichero et al., 2002). Since the mercury concentration in the blood decreased quickly and mercury was measurable within the stool, the authors of the study concluded: "This study gives comforting reassurance about the safety of ethyl mercury as a preservative in childhood vaccines." However, 8 days after vaccination the blood mercury levels were sufficient to kill neurons in vitro (Yel et al., 2005) or to significantly inhibit the production of methionine synthetase (Waly et al., 2004; Deth, 2004). Methionine syntethase is crucial for methylation and therefore for the development of the brain, for the maturation of nerve cells, for the production of neurotransmitters, and for producton of glutathione.

The risk for delayed neurodevelopment in children was 3.58 times higher if the cord blood had a higher level than 0.8 ng Hg/ml. Children whose mothers showed more than 0.5 ng Hg/ml in the their blood had a threefold increased risk compared to children from mothers with mercury blood mercury levels below 0.5 ng Hg/ml. (Jedrychowski et al., 2005). Numbers of maternal amalgam fillings correlate significantly with mercury levels in cord blood (Unuvar et al., 2007) and in fetal or infant tissues (Drasch et al., 1994).

In Germany, mercury levels of 0.2–5 ng Hg/ml cord blood seem to be the rule (Stoz et al., 1995).

Amalgam and Environment

As Clarkson and Magos (2006) report only few on the environmental impact of dental amalgam, we would like to provide some additional data on this important issue.

There was an alarmingly rising increase of mercury in our environment during the last decades. The United Nations Environmental Program (UNEP, 2002) reports a thre- to fivefold increase over the last 25 years.

In the Europaen Union (EU) the usage of amalgam amounts to 70 tons yearly. Dentist are the second highest user in the EU (Hylander and Godsite, 2006; Hylander et al., 2006).

Recent calculations done by Hylander (2005a, 2006) show that there are 40 tons of mercury in teeth in the dental amlagam of Swedish people, which results to the excretion of 100 kg mercury per year in wastewater; 1300 to 2200 tons of mercury in dental amalgam is present in the teeth of the citizens of the EU (Hylander et al., 2005b), and for the United States the respective figure is about 1000 tons. In the United States, dental amalgam is the third significant source of environmental mercury (Bender, 2005). In contrast to the EU, removed amalgam is not separated from the wastewater of dental clinics in the United States. But even in the EU, where such separators are in use, some of the dental amalgam leaks into the environment (Hylander, 2005a).

As this mercury from dental amalgam (mercury emissions from dental clinics in wastewater, excreted mercury emissions from amalgam in living individuals, mercury emissions from elevated mercury deposits in tissues of deceased and cremated humans with dental amalgam) will enter into the environment, Hylander and Godsite (2006) showed that amalgam is the most costly material for dental fillings, if environmental costs are included into the economic calculation.

CONCLUSION

Amalgam cannot be called a safe dental filling material as it was in the article by Clarkson and Magos (2006), neither with regard to medicine and occupational medicine, nor with regard to to ecology.

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