The dental amalgam issue. A review

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Summary. Using an interdisciplinary approach, the current position in the dental amalgam controversy and the potential impact of amalgam mercury on human health are reviewed. Aspects of materials science, corrosion, mercury exposure, toxicology, neurology and immunology are included.
New data on mercury exposure from corroded amalgam fillings in vivo are presented. The exposure can reach levels considerably over known threshold limit values. Also, measurements of mercury absorption from intraoral air are presented. The vital importance of avoiding a galvanic amalgam-gold coupling is emphasized. The symptomatology of a disabled patient, who recovered after amalgam removal, has been included.
It is concluded that discussion of the dental amalgam issue has suffered from the lack of an interdisciplinary approach. It would be wise to learn from the lesson of acrodynia, and consider amalgam mercury among other possible factors in neurological and immunological diseases of unclear etiology.
Key words. Dental amalgam; corrosion; mercury release; threshold values; toxicity; neurology; immunology.

1 Introduction

Amalgams are, in general, alloys of mercury with other metals. At the beginning of the 19th century, the idea of filling carious teeth cheaply and simply with mercury alloys spread from France and England to the USA and other countries. The first dental amalgams (ca 1818) were based on an alloy of bismuth, lead and tin, which had a melting point around 100 °C. Addition of a small amount of mercury decreased the melting temperature to 68 °C and thus also the suffering of the patient during the filling of the cavity.
In 1819, the chemist Bell started production of a silver-based amalgam. Around 1900, Black recommended an 'improved' high-silver alloy, which continued to be used as a basis for the most extensively used conventional filling material[130]. A pure copper amalgam was also in use until recently, often to fill children's teeth, in spite of its strong propensity to corrosion and related unfavourable performance and toxicity. In the 1970s, new copper-rich amalgams, called the non-gamma-2 type, have been introduced with the purpose of increasing the corrosion resistance of silver amalgam.
The use of amalgam for dental implants has been a subject of controversy throughout the 150 years of its extensive use. During the 'Amalgam War I' (ca 1830–1856) no dentist using amalgam was accepted as a member of the Society of Dental Surgeons in the USA. Due to the lack of alternative cheap filling materials the use of amalgam nevertheless continued, and the 'Amalgam War II' of the 1920s and 1930s revived the debate.
In Germany the distinguished chemist Alfred Stock contributed to the debate with many publications on amalgam and mercury toxicology and analytical determination, and also with a very informative description of his own chronic mercury poisoning[107,111]. In spite of its scientific background, Stock's warning that 'the thoughtless introduction of amalgam as a substance for filling teeth was a grave sin against humanity' has not influenced the dental profession. Surprisingly, no epidemiological evaluation of health status, for example of diseases such as neurasthenia, has been made in relation to the introduction of amalgam 150 years ago.
The medical use of mercury also initiated frequent debates. The insidious toxic effects were often very difficult to differentiate from the symptoms of the disease for which the metal was administered. One of the first careful descriptions of the symptoms of mercury poisoning was an attempt by Kussmaul[64]. The question was whether mercury poisoning produced symptoms distinctly different from those of syphilis, for which mercury was the preferred treatment. The study was carried out in mirror factories, where exposures were generally high, but already Kussmaul noted that sensitivity towards the metal was highly individual and unpredictable.
Today, extreme exposures as in the mirror factories are rare, but they do sometimes occur because of ignorance or accidents. Instead, most persons in the western world are chronically exposed to lower levels from dental amalgam fillings, often from childhood. In addition, anyone may be exposed to mercury in vaccines, drugs, contact lens solutions, cosmetics and, of course, food. Thus no single source can simply be dismissed as 'not more than a given level', but the sum of all sources has to be considered as a total load.
The degree of mercury exposure from amalgam has apparently been underestimated. A simple consideration of the amount of mercury in the teeth, compared to the daily intake from food, makes it apparent that amalgam would have to be an exceedingly stable alloy in order to contribute less mercury than the daily amount ingested with food. With 5 g mercury in the teeth (10 g amalgam), the fillings would last 1370 years if the release is a maximum of 10 µg Hg per day. 10 µg Hg is about what most people take in with food, if they do not eat too much fish. In southern Sweden the average daily intake was found to be 5.5 µg, but it was 12.4 µg with diets containing more than 75 g fish per day[27]. Amalgam fillings will some-

times remain in the teeth for 2–3 decades, but the average lifetime is considerably shorter. The 10-year survival rate for fillings in adults ranged from 13 to 74% in one study[78], others reported 50% replacement within 5 years and an average life span of 4–8 years[13]. In 6-year-old children the average survival time for occlusal amalgam fillings was 2 years and 2 months[132].

The terms 'silver filling' or 'amalgam' do not give a layman or non-chemist the important information about the 50% mercury content. Inorganic mercury has insidious effects, not readily recognized unless one is aware of the symptoms of chronic mercury exposure. Proper diagnosis will be even more difficult if the exposure is from amalgam fillings. To quote again from Stock[108], 'The dentists are seldom in a position to recognize the general effects of amalgam fillings or even learn about them. Patients suffering from nervousness, intellectual exhaustion, catarrh etc. usually do not complain to the dentist; in addition, they are prevented from talking during the treatment. They will rather discuss their problems with the family physician, neurologists, laryngologists and internists'. The physician in turn is completely unaware of dental treatments, and does not suspect mercury from amalgam. Thus it is not surprising that reports on mercury poisoning from amalgam are relatively rare in the medical literature. However, in the daily press and in magazines there have been numerous descriptions of health changes following amalgam removal.

There are many descriptions of the symptomatology of inorganic mercury intoxication, most of them written before interest was focused on methyl-mercury. Biochemists have also provided many studies on the cellular and molecular effects of mercury, providing explanations for many symptoms observed in clinical practice. Recently, the immunotoxic effects of mercury have attracted considerable attention. Nowadays, mercury is the best studied of the substances able to cause autoimmune disease. Immune reactions were also considered to be a factor in acrodynia of children observed after calomel (mercurous chloride) exposure. The acrodynia epidemic illustrates the puzzling nature of mercury intoxications. Even more puzzling is mankind's short memory after the discovery of the Hg-etiology of acrodynia. 'Man is apparently a poor student of history' as Casarett & Doull's 'Toxicology' says, referring to the use of mercury as a medicine.

In this review we will try to give an overall picture of the documented connections between mercury, especially in dental amalgams, and various possible neurological, immunological and orthomolecular effects. The fate of amalgam components other than mercury is not within the scope of this review. It is not possible to discuss every detail of this cross-scientific issue which touches not only odontology, but also materials science, toxicology, neurology, immunology, physical biology, analytical chemistry and diagnostics. The pertinent literature which we found to be available includes more than 8000 titles. This comprehensive bibliography is available from the authors. As well as reviewing the literature, we include new data of our own on mercury exposure, related to symptomatology, similar to that of chronic mercury poisoning, as known from occupational and accidental exposure. Further, measurements of mercury vapor absorption in the oral cavity are presented.

2 Structure and deterioration of dental amalgams

2.1 Structure

The conventional silver amalgam contains typically, in percentages by weight, 50 parts of Hg, 35 Ag, 10 Sn, Cu, Zn. The amalgamation reactions have been studied by Espevik[35] and can be described by the equation

$$Ag_3Sn + Hg \rightarrow Ag_2Hg_3 + Sn_{6-8}Hg$$

or:

gamma-phase + Hg → gamma-1 + gamma-2-phase

The reaction between the alloy powder (gamma) and mercury does not proceed stoichiometrically. Hence, both the composition and the amount of the structural phases in fillings vary depending on the overall composition, trituration time and insertion technique of the particular dentist. This is illustrated by the varying formulas reported for the gamma-1-phase:

Ag_3Hg_4, Ag_4Hg_5, Ag_2Hg_3, $Ag_{11}Hg_{15}$ and Ag_5Hg_8[130]

The corrosion sensitive phase gamma-2 has been described as Sn_7Hg, Sn_8Hg, Sn_{7-8}[35] and Sn_6Hg[74]. The content of the gamma-2 may vary between zero and 59%[14], but 15–20% seems to be frequent[89]. Normally, unreacted particles of the Ag_3Sn alloy are found after setting reactions. However, due to complicated and unpredictable setting reactions, free liquid mercury can also appear on polished surfaces of silver amalgam[99].

The preferential corrosion of the gamma-2 phase is partly responsible for the deterioration of conventional amalgam restorations. Therefore, attempts have been made to eliminate this phase by adding copper at concentrations of 6–15%[36]. These high-copper amalgam are called 'non-gamma-2'. The corrosion-prone phases in this system are CuSn[36] and the Ag-Hg-Sn phase[73].

2.2 Corrosion

Deterioration of various types of amalgam by electrochemical corrosion has been described in a large number of publications.

The documented types of deterioration are:
- crevice corrosion[35],
- selective corrosion[56, 57],
- galvanic corrosion in contact with dissimilar metals[40, 65, 66],
- stress corrosion cracking[37, 75],
- general corrosion[75],
- mechanical wear[26].

Mateer[75] investigated fifty extracted teeth containing amalgam restorations. Every restoration was attacked by corrosion, resulting in a surface layer of corrosion products. These observations have been consistently confirmed in the published literature and in clinical practice[36,47,62,89,97,100,120]. Corrosion may have advanced so that the amalgam has lost most of its strength[56]. For both mechanical and biological performance, avoidance of galvanic coupling to gold and other noble metals is of the utmost importance. Galvanic corrosion is also the only corrosion type which it is possible to avoid. The other types of attack, listed above, seem always to be present to some extent. The corrosion mechanisms of the non-gamma-2 amalgams differ from those of silver amalgam, but no clear model of their corrosion behavior has been presented.

The corrosion products of silver amalgam consist mainly of insoluble hydroxy-chlorides and oxides of tin[97]. As the products have a larger specific volume than the original alloy, they partly substitute for the released mercury and help to maintain the mechanical function of the filling. The crevice between tissue and filling may occasionally become sealed[75,131], but the voluminous corrosion products may also cause tooth cracking due to the high internal pressure[71].

3 Mercury exposure

A reliable knowledge of the exposure level is a prerequisite for any meaningful conclusion about the health hazard of amalgam in vivo. The traditional opinion of the dental profession during 150 years has been that amalgam becomes biologically inert as soon as it is set, i.e. in a few days[95]. A survey of the available data on metal release from dental restorations was published in 1986 by Brune[16]. The information available is rather sparse, and no investigation has taken into consideration all types of deterioration and routes of uptake in order to get the whole picture of the toxicological impact. Corrosion has been primarily considered with respect to the mechanical performance of the fillings. Despite the amount of published information about corrosion of amalgam, the toxicological impact of the released mercury has been discussed very little. Therefore, the question of mercury exposure will be treated in greater detail.

The lack of an interdisciplinary approach has tended to lead to underestimates of the mercury released from amalgam fillings in vivo. The work by Mayer and Diehl[76] provides an example. The investigators used oxygen-free distilled water for measurements of mercury released from amalgam. The elimination of any cathodic depolarizer, such as oxygen from the air, effectively removed the possibility of any corrosion process and led to a wrong conclusion about the high corrosion resistance of amalgam under conditions where oxygen is present.

The dissertation by Frykholm[43] has been used by dental professionals as a proof of the insignificant contribution of amalgam to the body burden of mercury. Frykholm did find increased urine mercury, and migration into dental pulp, days and weeks after insertion of amalgam, but he classified the amounts as insignificant. Frykholm's anticipation that the exposure to mercury released in mouth can be related to mercury found in the excreted urine does not find sufficient support in the literature. Until now, no defined partition of mercury between that excreted and that deposited in various organs has been measured, so it is not possible to judge the amount of dental mercury released from measuring the urine concentrations (see section on mercury in blood and urine). Therefore diagnosis cannot be based on urinary mercury determination. Frykholm's investigation of exposure during insertion and for a short time afterwards may not be relevant to long-term mercury release after the onset of corrosion in vivo.

Marek[72] observed an up to 56-fold (average 23-fold) increase of electrical corrosion currents during abrasion of five brands of fresh amalgams. According to Faraday's law, the measured corrosion currents corresponded to a daily release of 60–735 μg of mercury from 1 cm^2 of surface, assuming a total daily chewing time of 2 h[89].

In vivo, the two processes of corrosion and wear are interdependent[15], corrosion being strongly promoted by mechanical wear. To illustrate the possible toxicological impact of the volume of worn amalgam, it is of interest to consider the role of the wear process alone. DeLong[26] studied the wear rates in an artificial mouth, and found a correlation with clinical observations. At points of contact with enamel, a layer about 65 μm thick was worn away after 250,000 masticatory cycles per year. An assumption of a total contact surface in the mouth of 1 cm^2 then gives 6.5 mm^3 of worn amalgam, containing 37,000 μg mercury. As the tiny particles will be exposed to dissolution in the acidic stomach environment, the individual might be exposed to 101 μg Hg a day.

The most complete documentation of total mercury exposure and uptake up to now is that recently published by Hahn[48] and Vimy[127]. The radioactive labeled mercury from 12 fillings in sheep was determined by whole-body scanning and measurement in specific tissues. Mercury appeared within 29 days in various organs and tissues and in fetuses. The investigation confirms the three main ways of Hg-uptake; in the lung, the gastrointestinal tract and through jaw tissue absorption.

After one month, the total Hg content of the kidney was 1.86 mg and that of the liver 0.77 mg. Also the brain, pituitary, thyroid, pancreas and ovary glands showed evidence of Hg accumulation from dental amalgam. In addition to the deposited mercury, the sheep eliminated daily over 9 mg of Hg in 2000 g of feces. The order of magnitude is in reasonable agreement with the released amounts of mercury computed from Faraday's law and in vitro current measurements[89,72]. With 2 hour's chewing a day, 500–700 μg/cm^2 will be released from fresh conventional amalgam, i.e. 5–7 mg from 10 cm^2 surface.

Hahn's findings of dental mercury in tissues are consistent with analyses of mercury in autopsied human brains and kidneys by Nylander[82,83]. Subjects with amalgam fillings showed significantly increased Hg-contents in the pituitary gland, and the concentrations were related to the number of amalgam surfaces.

3.1 Mercury vapor

An amalgam bearer is exposed to a daily amount of mercury released from the fillings in the form of vapor, liquid metal and ions. A part of the released amount will be taken up by the body.

The main routes of uptake are:
- as metal and ions from the bottoms of fillings[120] and through the mucous membranes,
- as vapor in the lungs[86,51],
- in all forms in the gastrointestinal tract,
- by direct transport from the oro-nasal cavity to the brain[110,117].

The assay of mercury vapor Hg^o in the expired air of amalgam bearers is experimentally feasible, and it has been measured in a number of investigations. Stock demonstrated in 1926 that dental amalgam fillings generated mercury vapour in the mouth[107]. Chewing and abrasion[41,44,118,125], brushing[86] and increased temperature[121] strongly stimulated corrosion of amalgam and evaporation of mercury. Svare[118] measured on average a 15.6-fold increase of mercury in the expired air after chewing, compared to amalgam-free controls. The mercury content in exhaled air or in the oral cavity after chewing can exceed permissible industrial levels[86,118,125]. Stock's results inspired Brecht-Bergen[14] to measure the Hg-vapor pressure over amalgam:

Ag/Sn/Hg-alloy with 45% Hg:	10.7%	compared to pure Hg
Ag/Sn/Hg-alloy with 54% Hg	25.7%	compared to pure Hg
Sn/Hg-alloy with 30% Hg	54.7%	compared to pure Hg

Measuring the concentration of Hg in expired air or in the oral cavity leads to difficulties in calculating how much Hg is actually inhaled. Abraham[1] introduced flushing of the mouth for 15 s and measuring the evaporation rate from the fillings. A pre-chewing evaporation during 15 s was found to be 1.0–11.8 ng, i.e. 0.07–0.8 ng/s with a mean of 2.24 ng (0.15 ng/s). After 3-min chewing, the emission was 1.2–162.7 ng (0.08–10.8 ng/s) with a mean of 18.97 ng (1.27 ng/s). Berglund[9] found 0.16 ng/s (range 0.04–0.34) for unstimulated Hg-evaporation. The actual values after chewing might be even higher than those found by Abraham since the vapor levels continue to increase during 30 min of chewing[126]. Thus the evaporation rates from amalgam fillings in the oral cavity can reach 11 ng/s after chewing[1]. A comparison can be made with known evaporation rates from mercury. Pure Hg emits vapor at the rate of 2.5 ng/s cm^2 at room temperature and maximum air flow[113]. This will correspond to about 6 ng/s cm^2 at the oral temperature. Assuming an amalgam surface of 10 cm^2, the highest values recorded by Abraham will correspond to the vapor pressures measured by Brecht-Bergen[14].

Knappwost[60] measured the evaporation rate of mercury from 0.5 cm^2 amalgam in artificial saliva under static conditions. The evaporation levels were $0.66 \cdot 10^{-3}$ µg/s without, and ten times as much with contact with gold. From amalgam alone, the evaporation rate corresponds to an average exposure of 57 µg Hg a day. From 10 fillings of 0.5 cm^2 surface the exposure will be several hundreds µg a day. This is in good agreement with our own evaluation based on depth of corrosion[89] (this paper).

The evaporation depends on the vapor pressure, the flow of air over the surfaces, abrasion etc. The actual inhaled and absorbed amount of Hg is difficult to determine. However, nose versus mouth breathing does not seem to have a central role. To test for a possible direct oral absorption, we injected known amounts of mercury vapor into the closed oral cavity of an amalgam- and gold-free subject with no detectable mercury emission from lungs or oral cavity. After 0–3 min, air with the remaining mercury was sucked out and the mouth flushed with 30 ml of Hg-free air. An immediate extraction – within the first 3–5 s – showed an absorption of 5.5 ± 4.5 ng Hg (n = 6). Delayed extraction (1–3 min) resulted in steadily less Hg being recovered. In one series of experiments, 2.4-ml samples of Hg vapor from the mercury-saturated air over metallic Hg were injected. Mean absorption was 10.2 ± 2.1 ng/min (n = 12).

To obtain information on absorption kinetics, increasing amounts of Hg from 32 to 120 ng were injected and extracted after 1, 2 and 3 min (a total of 10 injections). The results indicate exponential absorption kinetics (table 1) and that most of the mercury vapor, generated from fillings in the mouth, might be absorbed even when chewing is done with closed mouth and nose breathing. The further fate of the absorbed mercury is unknown. Fredin[41], using a somewhat different approach, placed an inverted cup on the buccal oral mucosa and intro-

Table 1. a) Absorption of mercury vapor in the oral cavity. b) Absorption kinetics with increasing doses of mercury vapor. (Measurements by M. H.). Mercury determined with a Jerome Gold Film Mercury Analyzer, Modell 511. For experimental details, see 3.1.

Injected amount Hg ng ± SD	Mean absorption/min ng ± SD		
a) 32.9 ± 1.5	10.2 ± 2.1 n = 12		
b)	Non-absorbed Hg, extracted after 1–3 min ng Hg		
	1	2	3 min
32	14	8	5
42	21	13	10
79	34	31	22
120	--	--	39

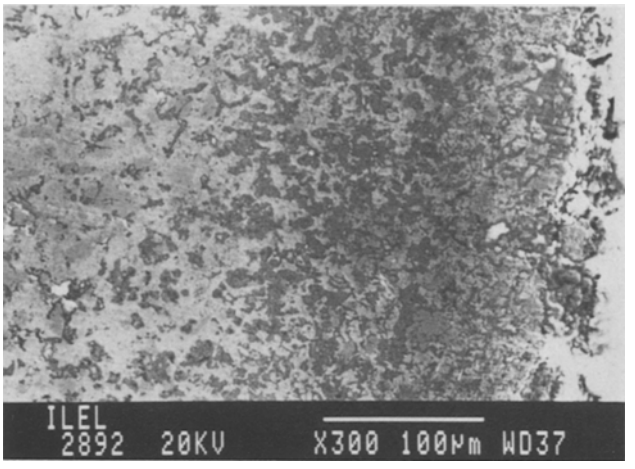
duced known amounts of mercury vapor. The results were similar to those described above. Hahn[48] also reported a high mercury content in the gum mucosa (323 ng Hg/g) of sheep with amalgam fillings.

3.2 The present authors' data on exposure

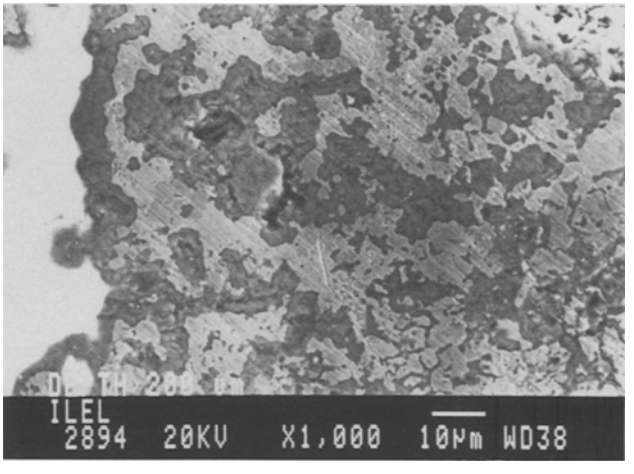
Twenty used restorations were investigated using a Scanning Electron Microscope (SEM, JEOL 940), equipped with an Energy Dispersive X-ray analytical device (EDX). The donors of the restorations belonged to a group of 250 patients with chronic health problems of unknown etiology. Information on age, sex, profession, medical history and dental treatment was obtained by a questionnaire. About 50 of these patients, who had had all their amalgam fillings removed (with initial aggravation of symptoms and, after a period ranging from several months up to a year, their alleviation) constituted a test group for possible mercury etiology. Patients who did not have their amalgam fillings removed served as one control group and 10 persons who had never had any such fillings as a second one. Persons with possible occupational exposure to mercury and those consuming fish from inland lakes more than twice a week were excluded from the investigation. A detailed evaluation of the patients will be published elsewhere.

From eighteen patients it was possible to recover pieces of large amalgam fillings, whole teeth with amalgam, or gold restorations in direct contact with amalgam. All were microscopically examined and figures 1–3 show typical examples. The type of corrosion attack was similar in all investigated amalgam fillings, though the severity of corrosion varied between specimens, probably depending on filling quality, age of filling, saliva composition and eating and chewing habits.

Figure 1 shows general corrosion of an amalgam surface 1.4 cm^2 in area, under a gold crown. This caused total release of mercury from a layer 100 µm thick, that is



a



b

Figure 2. *a* Cross-section through a silver amalgam filling after 8 years in vivo. The dark areas consist of converted amalgam products, free of mercury. This filling has been giving off 70 µg Hg a day.
b Photo 2894: Detail of the micrograph 2892 at a depth of 200 µm. The white area on the left is a cavity filled with corrosion products.

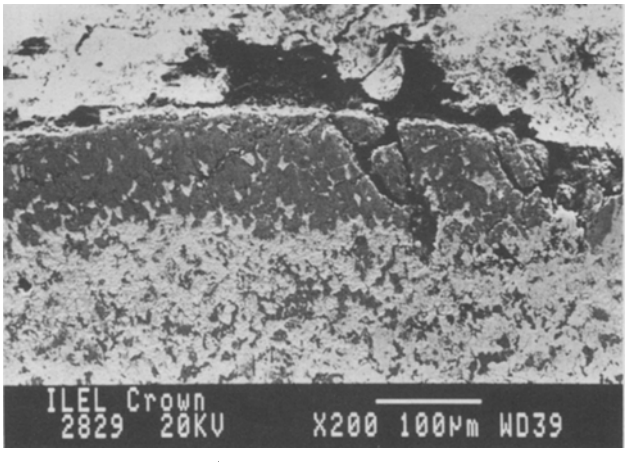


Figure 1. Cross-section through a silver amalgam filling under a gold crown after 9 years in vivo. The dark layer has been converted to corrosion products free of mercury. This filling has been giving off around 60 µg Hg per day.

68 mg in 9 years, i.e. 29 µg Hg a day. In addition, selective corrosion throughout the amalgam is estimated to have released at least another 30 µg Hg a day. The total average exposure from this restoration was about 60 µg, and from all the fillings of this patient at least 150 µg per day.

Another example of a strongly corroded filling shown in figure 2 had released 102 mg of Hg in 8 years, i.e. 70 µg a day. Corrosion has penetrated the filling, creating narrow channels. The dark products in the channels are free of mercury, as confirmed by the EDX-analysis. The comparison of the spectra of the bright and dark phases is shown in figure 4. The corrosion products consist mainly of tin oxides and hydroxides, but silver, sulphur and chloride were also found, indicating silver sulphide and/or chloride.

Figure 3 shows the buccal surface of an amalgam filling without contact with gold after 5 years in vivo. The sur-

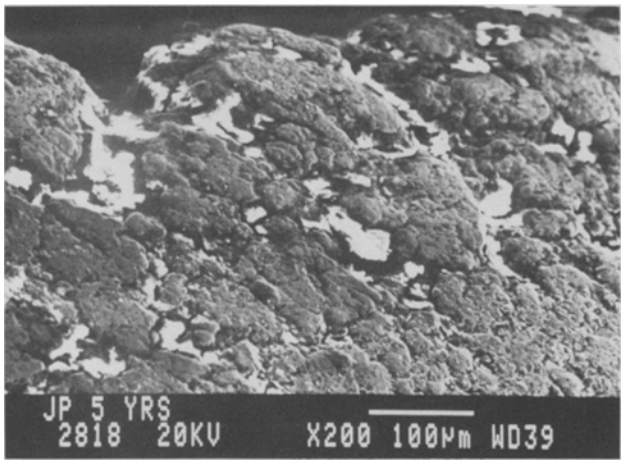


Figure 3. Appearance of the buccal surface of a filling after 5 years in vivo. The mercury-depleted surface layer is 14 µm thick, and the selective attack has released over 8 µg Hg a day.

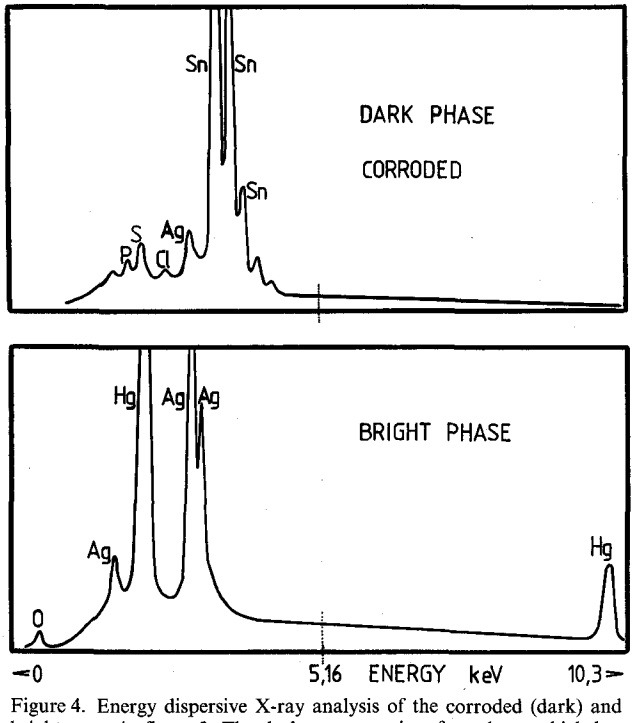


Figure 4. Energy dispersive X-ray analysis of the corroded (dark) and bright areas in figure 2. The dark areas consist of amalgam which has been converted to mercury-free corrosion products. Similar spectra have been obtained from the dark and bright areas in figure 1.

All scanning electron micrographs and EDX-spectra by J. Pleva.

face has been corroded and totally depleted of mercury to a depth of 14 µm. From 1 cm^2, 9.5 mg Hg was set free in 5 years, that is 5.2 µg Hg a day. The selective attack on the gamma-2 phase has been estimated to have given off additionally 3 µg a day. In this patient, the total exposure from 10 cm^2 of corroded surface was 82 µg Hg per day, not counting unknown amounts from the abraded layer and release from fillings in contact with gold restorations.

Figures 1 and 2 confirm previous findings by Sarkar[97] that the corrosion process can be a process of conversion rather than dissolution. The filling is slowly converted to products of constantly decreasing mercury content, while the volume remains substantially constant. The converted products still fill up the space even when mercury is no longer present, and no obvious change is apparent to the eye or on routine examination by light microscopy. The replacement of amalgam by more voluminous corrosion products explains the apparent contradiction between the constant volume of old fillings and the simultaneously-reported high release of mercury and its health effects.

3.3 Case history

The person from whom the fillings illustrated in figures 1 and 2 were removed was a Swedish woman, 58 years old, a telephone operator, retired at age 40 because of disabling chronic health problems. The syndrome included 24 symptoms of mainly somatic character: diarrhea with strong bleeding, joint-, muscle- and back pains, frequent inflammations in eyes and upper respiratory passages, sinusitis, severe fatigue, stress, loss of memory, vertigo, impaired hearing, increased salivation, bleeding gums, asthma, irregular heart-beat, heart and chest pains, disturbed sleep and eczema.

The official diagnosis was Morbus Crohn with rheumatic and allergic affliction of intestines (organic enteritis), joints, eyes and upper respiratory passages. The etiology was not known. Dental status: since childhood amalgam fillings in most teeth; a short time before the severe disease manifestations she was given gold restorations which were in contact with amalgam.

When interviewed in 1990, four years after amalgam removal, she reported amazing recovery with only 4 weak symptoms left: fatigue, eczema, occasional diarrhea and impaired ability to concentrate. The woman was one of the 250 patients (see 3.2) with similar symptoms. Three other cases are described in Pleva[89].

3.4 Comparison with literature data

Comparison of the above results with published investigations confirms the considerably high mercury release under realistic conditions[15,48,60]. The common denominator of many published investigations is the use of fresh amalgam, i.e. amalgam which is only at the start of its deterioration process[15,36,40,62,72,76,99]. The daily release of 9 mg of Hg, which was found by Hahn[48] in investigations of the feces of sheep one month after the insertion of 12 fillings, would have consumed all the mercury in less than 2 years. As this rate of loss has not been observed in practice, either the release must decline after some months, or the filling will loosen and be replaced by a new one in a relatively short time.

Considering the strong variations of the Hg-content in the feces of amalgam bearers[12,112], mercury excretion due to oral corrosion may vary appreciably. Stock[112] reported daily amounts between 10 and 56 µg Hg in feces and urine, compared to the average 3.5 µg Hg of controls. No data about number and size of the fillings are given.

Borinski[12] also states that excretion (urine + feces) of 5–10 µg Hg a day is frequent in amalgam-free subjects not exposed to mercury except from food. Borinski discovered the ubiquitous occurrence of mercury. Excretion over 10 µg indicates an exposure level considered to be potentially harmful. After insertion of an amalgam filling, strongly increased excretion of Hg was observed during some months, after which the excretion decreased. During the first three months, about half of the test children showed a total daily excretion in the region of 10–100 µg, the other half over 100 µg Hg. From Borinski's text it is apparent that most of the test subjects were treated with one filling only. From the above, and from Kozonos'[62] investigations, it is apparent that the mercury release is highest in the first months after insertion and decreases with time. The decrease of the decay depends on the build-up of corrosion products, impeding the transport of mercury and other species between the inner parts of fillings and a non-abraded surface. Also the decreasing concentration of mercury in the filling will lower its diffusion rate to the surface. However, after a longer time the metal release may increase again[62].

The Swedish 'standard man' for discussion of dental restorations has been defined as an adult aged 40–50 years, with 16 amalgam restorations with a normalized occlusal geometrical surface area of 10 cm^2,[84]. A part of the hidden surfaces (bottoms of fillings) is subject to crevice corrosion. Therefore, to obtain the total surface releasing mercury, the occlusal surfaces need to be multiplied by a factor larger than 1.

3.5 Mercury in blood and urine

'Normal' values for mercury in blood and urine (B + U) were found in the sheep with amalgam fillings, whereas the tissue and feces levels were high[48]. The first reliable measurements of Hg in B + U demonstrated that blood values remained low until the exposure level became high. Little increase was found in the urine, but much higher levels in the feces[112]. Some studies show that amalgam fillings do have a certain effect on blood Hg-levels[105] and that removal of amalgam fillings reduces the Hg-level[105]. Other studies found no difference[63]. Amalgam placement causes a transient peak of mercury in the urine[43,98,114].

Human experiments with single doses of swallowed radioactive ionic or inhaled elemental mercury show that 1–2% of the absorbed dose is eliminated in the urine in the course of a week after the exposure[21,91]. The observed urinary excretion after amalgam placement thus corresponds to several mg of total absorption. Recent studies show that the number of amalgam fillings is positively correlated with urinary mercury[69]. Few measurements of fecal mercury levels have been made. Tompsett and Smith[122] found levels of 50–180 µg a day, without considering amalgam fillings as a source. Lamm and Pratt[67] found a significant negative correlation between exposure time of workers and urinary excretion of mercury, indicating impaired urinary excretion of the metal. The investigators found a positive relation between time at work and subclinical neurological damage. Administration of dimercaptopropane sulphonate (DMPS), a heavy metal chelator, produced a massive increase of mercury excretion in amalgam exposed patients with low, 'normal' Hg levels in urine[25]. In the Soviet Union, DMPS is used for diagnostic purposes. An eight times increased urinary Hg-excretion after chelation is considered to be indicative of adverse Hg-effects, when symptoms of 'micromercurialism' are present[42].

There are several uncertainties regarding the use of B + U Hg-levels as diagnostic tools. Most industrial studies relate the B + U-levels to the percentage of affected workers, irrespective of the severity of symptoms. The adverse effects of long-term exposure to low levels of mercury – 'micromercurialism' – can be completely devastating for the affected individual, as was vividly described by Stock in 1926[107].

Detailed investigations on single blood cells with proton-induced X-ray emission equipment demonstrated that only some of the thrombocytes and red and white cells in patients with suspected amalgam poisoning contained mercury[4]. In a healthy control population the mercury levels in all cells were below the detection limit. Only one controlled study on animals has assessed blood Hg-levels in relation to mercury levels in inhaled air[34]. Blood Hg was found to be related exponentially to the exposure level. Assuming that a similar situation exists in humans, blood Hg levels would be expected to show moderate changes within a broad range of levels of exposure.

Chlorine gas reacts spontaneously with Hg^0 vapor in the air[46]. Already in 1904 it was recognized that the best method of protecting workers in mercury mirror factories was to maintain a low chlorine content in the air[24]. The elemental mercury is then oxidized to the much less toxic mercurous chloride (calomel). Viola[128] and Viola and Cassano[129] found precipitated calomel in mercury-using chlorine factories. They also studied rats exposed to mercury vapor in comparison to exposure to air with a mixture of mercury and chlorine. Exposure to the mixture in the same proportions as in the chlorine factories, but at higher levels, was strikingly less toxic than exposure to Hg alone. Whereas the rats exposed to Hg alone suffered severe neurological symptoms, those exposed to Hg + chlorine only showed mild gastrointestinal disorders. The difference in symptomatology can be explained by the fact that the brains and hearts of the rats exposed to both Hg and chlorine had only 8–10% of the levels found in rats exposed to Hg only. Total body uptake in the doubly-exposed rats was 60% compared to Hg-only rats.

4 Amalgam poisoning

Mercury poisoning from amalgam fillings has been described several times. Stock[108] relates cases with devas-

tating psychic effects, and also aggravated symptoms when fillings were drilled out without suction. Further cases have been described by Stock[109,111]. Fleischmann[39] reported that conditions for poisoning were present in carriers of copper amalgam fillings (as judged from the Hg-values in urine and feces), whereas no conclusion could be reached for silver amalgam. Fleischmann found that the disappearance of symptoms after the removal of silver amalgam indicated that poisoning could occur. Harndt[49], studying the same patients, considered patients with gold in contact with amalgam as self-evident poisoning cases since the enhanced corrosion could clearly release enough Hg. Other cases have been presented by Wesselhaeft[136], Hyams[52], Steffensen[106], Lain and Caughron[65], Struntz[115], Rost[94], Zamm[137], Pleva[88] and Daunderer[25].

Effects of amalgam removal or placement on T-cells in 3 patients (one with multiple sclerosis, MS) was measured by Eggleston[33], and the acute exacerbation of MS-symptoms during removal (pulverization) of one old filling was reported by Ingalls[53]. Taskinen[119] followed a patient who had fillings ground to form a bar to support a bridge. In addition, 11 fillings had about 1 mm ground away to improve occlusion, and three fillings were replaced during the following session. After a week, the patient developed stomatitis, a sore throat, a rancid taste in the mouth, loss of the sense of smell, dizziness and headache, and later pains in the thorax, fever, elevated sedimentation rate, weakened sense of touch in her left hand, sensitivity to cold in the fingers, and a weakened hand grip. The patient felt rather bad, lost 9 kg of weight and became anxious and depressed. The fillings had been removed with extreme caution. The authors find that the symptoms correspond to those of micromercurialism.

Anorexia hydrargyria was described in a 15-year-old girl[31], who developed headache, joint pains, vertigo, loss of memory, fatigue, sleep disturbances and hair loss. Lack of appetite led to loss of weight and symptoms of anorexia nervosa. There were, however, no psychic problems. The physician noticed that the patient's mouth contained 10 glittering amalgam fillings. At an early school age, the patient had received 6–8 fillings, with no effects on her health. In 1986 the fillings were all replaced by new ones and new ones added. The girl was treated with dimercaptopropane sulphonate and the fillings removed. This treatment brought about a complete recovery. The author of the report considers the current toxicity evaluation by the dental authorities as insufficient. Diffusion of mercury through the pulp, the number and quality of the fillings and the toxicity of amalgam for pregnant women, children and adolescents have not been taken into consideration.

Studies of the relationship between the number of amalgam fillings and impairment of health do not show any differences. Ahlqwist[3] studied 1024 women, aged 38–72 years. No difference was found between persons with 1–4 amalgam fillings and persons with more, when the number of teeth was used as a corrective variable. Time factors were not studied, neither was there any information on gold-amalgam combinations or other types of dental restorations. It is not likely that middle-aged persons in Sweden will have many intact teeth. Lavstedt and Sundberg[70] could not find any correlation between the prevalence of mercury-related symptoms and the number of amalgam surfaces. Hugoson[50] found only a few cases among 100 patients whose symptoms could be attributed to reactions to dental restorative materials.

In a study by Jontell[54], 62 patients with 'oral galvanism' were studied. The authors conclude that most symptoms could be ascribed to psychosocial factors. Blood mercury measurements showed no differences between the patient and control groups. Müller-Fahlbusch and Wöhning[80] also ascribed the symptoms of 50 patients, who suspected amalgam poisoning, to psychogenic factors. Removal of amalgam led to an aggravation of the symptoms in 28 of 29 cases. Three of the patients had new, allegedly improved, amalgam fillings. There is no information on protective measures during the amalgam removal, on whether the aggravation was immediate, or on later changes in health. In one county in Sweden, 248 patients were referred to the specialist dental clinic for possible amalgam-related problems. They were questioned after 1/2 to 3 years about treatment and possible health changes. Most of the patients had exchanged the amalgam fillings. Total amalgam removal gave significantly better results than other types of treatment or no treatment, the former having hardly any effect at all. Improvements ranged from 85% for oral symptoms, 75% for headache to 66% for psychic problems. The authors consider the improvements real. However, they ascribe them to placebo effects, since so many symptoms disappeared[59].

5 Mercury toxicity and symptomatology

The toxicity of inorganic mercury has been described several times in the course of centuries. The most common form of exposure is inhalation of vapor. There is general agreement that inhalation leads to a slowly-developing and insidious poisoning which primarily produces psychic effects, and is very difficult to recognize until more objective symptoms appear. Numerous more-or-less extensive descriptions can be found in the literature. Baader[5] has described the major symptoms: Stomatitis, gingivitis, loose teeth, salivation or dry mouth, foul breath, metallic taste, redness in the throat, black line along the teeth, diarrhea, speech problems, nephritis, anemia, relative lymphocytosis, pressure over the chest, irregular heart, circulation disturbances, low blood pressure, increased sweating, disturbed sleeping, tremor, shaky handwriting, dull pains in limbs and joints, fatigue, headache, anxious seclusion, uncertainty, shyness, labile mood, agony, forgetfulness, feeling of intellectual ex-

haustion, sensory disturbances of skin, irregular menstruation, thyroid disorder, eye pigmentation, eczema. Common misdiagnoses are neurasthenia, hysteria, schizophrenia. Other symptom descriptions can be found in Schulz[101], Burgener[17], Oettingen[85], Nordin[81], Moeschlin[79] and Poulson[90].

In addition to the general symptoms of mercury poisoning there are numerous reports on individual cases of less common forms of poisoning, which are likely to pass unnoticed in industry. The largest such study involved only about 600 workers in the chlorine industry[104]. The types of symptoms depend on the mercury compound and the mode of administration. An amyotrophic lateral sclerosis-like (ALS-like) syndrome has been reported after exposure to ethylmercury[58], mercury vapor[2] and inhaled mercuric oxide[8]. Redhe[92] described the complete recovery of a 29-year-old woman with an official ALS-diagnosis, after all amalgam fillings had been removed.

Mercury-neurasthenia has been known for a long time. Various forms of paralysis, affecting different parts of the nervous system and diagnosed under different names, have been reported: polyradiculoneuritis, Guillain-Barre' syndrome, and multiple sclerosis[6, 11, 64, 138]. If the mercury exposure is recognized and interrupted, most cases recover, some slowly, but many surprisingly rapidly.

When the mercury etiology of acrodynia was clarified, the possibility that MS was an adult form of acrodynia, and a neuroallergic reaction, was considered. Baasch[7] recognized the possibility that amalgam fillings could be the responsible source of Hg. He concluded that the amalgam mercury etiology could explain the known facts about MS. Baasch noted the presence or absence of amalgam fillings in 500 consecutive MS patients in Zürich. All but one (or possibly two) had amalgam fillings. However, amalgam fillings are common, so this finding proved nothing. On the other hand, there are also other sources of mercury. Three cases were described by Baasch. Two of these had their amalgam fillings removed and the patients improved. The third one showed a rapidly developing disease, starting a few months after she got her first amalgam fillings at 19 years of age. When 8 years old she had been treated with mercury for congenital syphilis.

Knolle and Günther[61] described the mercury/amalgam status of 100 MS patients. Eleven of these had previously been treated with mercury ointments. Seven had no teeth, and the percentage with amalgam did not differ from that in the general population. The high percentage of mercury-treated patients seems to be remarkable. Stutte and Groh[116] discuss an acrodynia case with paralysis, caused by the rectal administration of metallic mercury in vaseline, and the suspected mechanisms behind this kind of 'idiosyncrasy'. The proposed sequence of events in acrodynia was suggested to be an initial attack by mercury on the blood-brain/nerve endothelial cells with a secondary immune reaction to brain components.

Oral or subcutaneous mercuric chloride in rats was found to cause a long-lasting but not permanent impairment of the blood-brain barrier with extravasation of plasma components[19], demonstrating that acute or subacute exposure could expose the immune system to neuronal antigens.

Stock[107] published one of the few descriptions of how it feels to be poisoned by mercury. He emphasized the psychic effects, which were especially troublesome for an intellectual. In addition to a number of somatic symptoms, Stock mentions: 'Intellectual exhaustion and depression, lack of energy and working ability, especially for intellectual work, increased need for sleep... For a person with intellectual work, the loss of memory was the most severe burden. Especially the ability to calculate and to perform mathematical thinking, also to play chess, was severely affected. The lowered ability to remember and the difficulties in calculating seem to be a special sign of insidious mercury vapor poisoning. The intellectual capacity was depressed in other ways as well, although not as much as the memory. In addition there was psychic depression and painful inner restlessness, with time causing disturbed sleep. By nature fond of company, and enjoying life, I withdrew depressed into myself, avoiding public relations, people and social contacts. I lost the love for art and nature. Humor became rusty. Difficulties, previously cleared with ease, (as they are again today), appeared insurmountable. Scientific work required considerable effort. I forced myself into my laboratory but could not produce anything of value despite all efforts. My thoughts were heavy and pedantic. I had to give up participating in matters of no immediate importance. The lectures, previously something I liked, became tormenting. The preparation of a lecture, the writing of a paper, even a simple letter, required immense efforts in handling the contents and language. Not seldom I happened to write words in the wrong way or forgot letters. To be aware of these shortcomings, without knowing their cause, seeing no way to get rid of them, expecting further aggravation – that was not nice!'

Three cases among dentists have been described by Smith[103]. The first dentist had hand tremor, impaired motor control, indifference towards family and friends and a visual disturbance. The subjects experienced irritability, critical excitability, fearfulness, restlessness, melancholy, depression, weakness, timidity, fatigue, indecisiveness and headache. The dentists emphasized that the mental effects of mercury poisoning were most distressing and frightening. Being deeply affected by the feeling of a hopeless situation, depression and futility, they urged the physician to bring the cases to the attention of the medical profession.

6 Mercury and immunology

Mercury is well known to be immunotoxic. Inhalation or swallowing of mercuric chloride or methylmercury, in

doses comparable to industrial exposures or intake in food, results in the same systemic autoimmune reactions which occur after subcutaneous administration in susceptible rat strains [10]. The autoimmune disease is characterized by antibodies to a variety of proteins, mainly of endothelial origin [96]. Outbred animals show a more complicated response [28, 93]. The effects on the immune system are thought to be mediated by interaction between mercury and T-cells. The result is a genetically determined, polyclonal activation of B-cells [87]. The Hg-induced autoimmune disease shows the same types of autoantibodies as in a number of human diseases, graft vs host disease and reactions to some drugs [32]. Long-term exposure of rats and rabbits to low levels of Hg-vapor, 6–10 $\mu g/m^3$, for 6 h a day, caused first a stimulation of the immune response and a decline after months [123]. Trachtenberg finds that the immunological changes occur significantly earlier than other signs of latent toxic effects.

A recent study on human granulocytes demonstrated that exceedingly small amounts of Hg are required to stimulate oxygen free-radical production from neutrophils (PMNs) in vitro, and to depress various other PMN functions [23]. The radical production was increased at 10^{-17} M, reached a maximum at 10^{-13} M and almost disappeared at 10^{-7} M concentration. In vivo, the presence of sulfhydryl groups in blood proteins might change the figures considerably by non-specific binding of Hg. Also, free radical production and DNA single strand breaks in hamster ovary cells, induced by mercury, showed a distinctly nonlinear response [18]. Release of oxygen free radicals is suspected of mediating the pathological effects of adverse drug hypersensitivity reactions [124]. Skin hypersensitivity to mercury has been reported to occur in up to 26.6% of the population [29]. There is a limited number of described cases of skin reactions caused by amalgam fillings. There is no indication that skin tests for mercury would give any information on systemic or immunotoxic effects of mercury. Stock, who was hypersensitive to traces of inhaled mercury, showed no positive skin reaction. Children with acrodynia seldom gave a positive reaction [134]. Fanconi [38] observed that in children who were exposed to calomel parenterally, a positive skin reaction could sometimes be shown when the calomel-disease was at its peak. A few weeks later, a new test was negative. Children with a negative patch-test could develop a flare-up at the site of the previously negative Hg application when they accidentally swallowed another dose of calomel. Some children developed systemic hypersensitivity after calomel treatment, but some became more resistant to a second dose. Baader and Holstein [6] report that occupational exposure leads to increased sensitivity towards further exposure. The acquired 'idiosyncrasy' is often the only permanent effect of mercury poisoning. Stock [110] describes the slow development of mercury sensibilization: 'To provoke a first reaction to mercury vapor, a stronger and longer exposure is required than what is needed for following exposures. Later on, symptoms can appear within an hour after exposure to much lower levels. If further exposure is avoided, the sensitivity slowly disappears, more so if the poisoning has been severe and prolonged. Recovery can take years.'

Mercury has a strong affinity for sulfhydryl groups and it is generally assumed that inhaled mercury is rapidly ionized in the blood and binds to SH-groups of enzymes. Exposure of animals or humans will lead to a measurable reduction of free tissue and blood sulfhydryl groups. A simple estimate, however, will lead to the conclusion that even with fatal kidney levels of Hg there will not be enough metal to bind to more than 10% of available sulfhydryl groups [22]. Glutathione levels alone are in the millimolar range. A catalytic oxidation of sulfhydryl groups by one mercury ion seems to be a plausible explanation. Mercury is known to release calcium from mitochondrial stores [20], an effect of free radical chemistry known to involve oxidation of thiol groups [102]. Glutathione reductase is inhibited up to 15% by 13 ng Hg/ml (67×10^{-9} M), and myelin phosphodiesterase up to 40% by 100 ng Hg/ml [30, 135]. The levels of mercury in the brains of humans with amalgam fillings are proportional to the number of fillings, and are within the range mentioned [82].

7 The acrodynia lesson

The best studied cases of human mercury poisonings come from the now almost forgotten disease acrodynia. This disease, mostly affecting children, was first recognized in France in 1828. It reached epidemic forms in some parts of the world. The skin on children's fingers and toes was particularly affected and peeled off. The skin appearance gave the illness the name 'pink disease'. The patients suffered from pains in the limbs and circulation troubles, and in extreme cases fingers and toes could be lost. Extreme weakness of the muscles, weight loss, sleep and gastrointestinal disturbances, tremor, chorea, sometimes fever and conjunctivitis belonged to the clinical picture. Some patients developed salivation, loose teeth and necrosis of the jaw bones. Thousands of children died. Many causes have been suggested: lack of vitamins, endocrine disorders, allergy, hysteria, neurosis, mold poisons and viruses. Mercury etiology was first suggested in 1846. Again in 1922 a physician pointed out the similarities with mercury poisoning. In 1945 Warkany [133, 134] found that in almost every case of acrodynia, mercury exposure could be demonstrated. The most common exposure sources were teething powders containing calomel, and calomel-containing preparations against gastrointestinal parasites.

Warkany and Hubbard, in 1953 [134], and Warkany in 1966 [133], pointed out that although the administration of these mercury preparations was frequent, only a fraction of the exposed children developed acrodynia. They calcu-

lated the incidence to be about one in 500. Mercury excretion was often found in controls as well, although no symptoms were present. Despite the exposure, mercury was not always detected in the urine samples of acrodynia children. However, careful studies showed mercury exposure in every case. Warkany notes: 'It seems rather odd that one could not detect the injurious mercury at the entrance to the alimentary canal, whereas it could be demonstrated at the end of the urinary tract.' Pseudo-acrodynia with some features of the real disease was produced by different treatments in animals. However, 'a subtle, complicated, and no doubt molecular disease was eradicated by such a prosaic measure as removing calomel from old-fashioned teething powders and worm medicines. There were data on electrolyte changes, explaining the symptoms of acrodynia and their alleviation by subtle saline treatments. But these data did not take into account the one electrolyte that mattered, namely mercury'[133].

8 Threshold limit values – How much mercury is too much?

Safety evaluations for inorganic mercury are based on industrial observations, and for amalgam specifically, on estimates of the exposure levels from amalgam compared to the industrial MAC-values (Maximum Allowable Concentration, comparable with the concept of Threshold Limit Values, TLV, used in the USA). In the USA, most government agencies recommend a maximum of 50 μg Hg/m^3 in industry, based on the study of Smith et al.[104]. A review of the subject[139] shows that the U.S. EPA (Environmental Protection Agency) National Emission Standard, 1 μg Hg/m^3 for mercury as a hazardous air pollutant, is the only air-exposure standard based on studies of the effects of mercury on the general population, and not limited to a 40-h week. In the Soviet Union, the corresponding value is 0.3 μg Hg/m^3, based on thorough studies of chronic mercury exposures by Trachtenberg[123].

As shown in table 2, estimates of safe industrial exposure levels vary between different countries by an order of magnitude. In some countries, the safety limits for the general population are 30–50 times lower than the industrial limits.

The MAC-values are defined as: that average concentration in the air which causes no signs or symptoms of illness or physical impairment in all but hypersensitive workers during their working day, on a continuous basis, as judged by the most sensitive internationally accepted tests[77]. Hypersensitivity is not stated to be evidenced only as skin reactions. No regulation for any mercury compound considers additional exposures, or the possibility of reduced resistance due to low dietary levels of selenium, zinc and other essential substances which are known to counteract mercury effects. The occupational TLVs are not relevant for the general population for the following main reasons: There is (or should be) regular medical control of occupationally exposed workers, and suspected mercury-related problems can be alleviated by changing the working conditions. TLVs for mercury are based on studies in the electrolytic chlorine industry where the workers are to some extent protected by the oxidative effect of chlorine on mercury vapor (see section on Hg in blood and urine). The TLVs may therefore be too high for continuous exposure in chlorine-free air. For the general population, it is also necessary to consider individual sensitivity, chronic diseases, and effects on children, pregnant women and elderly people.

Table 2. Examples of Threshold Limit Values (TLV or MAC) for mercury in air and food. Exposure amounts of mercury are given in each case. Presumption: respiration volume/rate: 0.75 l/15 per min. About 80% of the respired mercury is taken up in the lungs[51].

Occupational exposure 8 h/day, 40 h/week	TLV/MAC μg Hg/m^3	Exposure calculated from respired air and Hg level; μg Hg/day
Germany	100	540
Sweden	50	270
World Health Organization (WHO)	25	135
Soviet Union	10	54
General population, 24 h/day		
EPA, USA	1	16.2
Soviet Union	0.3	4.8
Exposure from food		
Sweden	30 μg/day	30

9 Conclusion

The puzzling insidious biological effects of various forms of mercury are often difficult to recognize when correct data on mercury exposure are not considered. The disease of acrodynia may serve as an illustration. Besides the diagnostic difficulties, the dental amalgam debate has been affected by the lack of an interdisciplinary approach. Despite a large number of specialized papers on amalgam, very few attempts have been made to relate clinically observed deterioration and wear of amalgam restorations with estimates of metal release, which can also be made from such studies. Corrosion currents have been measured in vitro, but this has not led to the obvious step of using Faraday's law to calculate the corresponding metal release; instead, it has led to a strange discussion on 'oral galvanism' and the possible biological effects of the generated currents. It is clear from known facts, and using available scientific and technical methods, that estimated exposure levels for mercury will be found to be higher than was previously thought. The conclusion is that such levels could have considerable toxicological and immunological consequences. A review of the controversy indicates a serious deficiency in the efforts of the dental profession to test the published warnings, for example those of Professor Stock, and to bring clarity into the issue.

Recent investigations on the fate of amalgam mercury, using whole body image scans[48], show that in sheep mercury release of up to 1 mg a day from one filling is possible during the first months after insertion. Sheep were chosen as experimental animals since they use molar chewing as do humans[48]. Some humans use chewing-gum or exhibit bruxism (grinding of the teeth), and might abrade their fillings as much as sheep fed two meals a day. Further, investigations of amalgam restorations after a known time in vivo show that the amount of mercury released can reach levels several times higher than accepted threshold values. The corrosion process may not be apparent to the eye, as it is a matter of amalgam conversion rather than dissolution. The extensive published knowledge about mercury toxicology indicates that toxic effects from amalgam mercury cannot be excluded. Immunological disorders can appear at considerably lower exposures than those from dental amalgam. Comparison with occupational threshold limits for mercury suggests that amalgam bearers should be under regular medical surveillance in the same way as mercury-exposed workers.

A comprehensive bibliography with over 8000 titles on mercury and its health effects can be obtained from the authors.

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The human leukemia cell line, THP-1: A multifacetted model for the study of monocyte-macrophage differentiation

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Summary. THP-1 is a human monocytic leukemia cell line. After treatment with phorbol esters, THP-1 cells differentiate into macrophage-like cells which mimic native monocyte-derived macrophages in several respects. Compared to other human myeloid cell lines, such as HL-60, U937, KG-1, or HEL cell lines, differentiated THP-1 cells behave more like native monocyte-derived macrophages. Because of these characteristics, the THP-1 cell line provides a valuable model for studying the mechanisms involved in macrophage differentiation, and for exploring the regulation of macrophage-specific genes as they relate to physiological functions displayed by these cells.
Key words. Atherosclerosis; cellular differentiation; gene expression; foam cells; lipoproteins; phorbol esters; transcription factors.

The mononuclear-phagocyte system

The 'mononuclear-phagocyte system' consists of tissue macrophages and their precursor cells, monocytes[105]. These cells are considered to be a 'system' because of their common origin, their similar morphology, and their common functions, including rapid phagocytosis. This 'system' is dynamic and is represented in almost all tis-