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IMMUNOLOGICAL EFFECTS OF MERCURY

(IUPAC Technical Report)

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Abstract: Various chemical species of mercury differ considerably with regard to their route of absorption and their distribution in the body, yet many of them and their metabolites exhibit high-affinity binding to sulfanyl groups of proteins. Among all metals, mercury appears to have the most diverse effects on the immune system. Depending on the animal species and experimental conditions, mercury compounds may cause immunosuppression or immunostimulation, autoimmune reactions, or hypersensitivity. Mercury-sensitive strains of rats and mice are often used as model organisms to study the time course and events in autoimmunity. Within about 14 days after onset of oral mercury(II) exposure, levels of immunoglobulins E and G (IgE and IgG) increase, including autoantibodies to biomolecules such as laminin and fibrillarin. Antigen-antibody complexes are formed and are the cause of subsequent autoimmune diseases of blood vessels and organs. Mercury may induce local mercury hypersensitivity in humans, but the evidence for a role of mercury in autoimmune disease of humans is at best weak. Models for the immune effects of mercury are presented on the basis of current knowledge.

Keywords: immunosuppression; immunostimulation; mercury immunology; mercury hypersensitivity; autoimmune disease; IgE; IgG; laminin; fibrillarin; IUPAC Chemistry and Human Health Division.

INTRODUCTION

Mercury compounds had many industrial and pharmaceutical applications in previous centuries. However, due to the toxicity of both inorganic and organic (e.g., methylated) species of mercury to various organs such as the brain and the kidneys [1–4], the usage of mercury was progressively restricted. The major source of exposure to inorganic mercury today is probably from its use in dental amalgams [5,6], and the mercury body burden increases with number and lower quality of fillings. The major source of organic mercury is the consumption of fish [7,8]. International efforts to further reduce mercury usage and its release into the environment are in progress [9]. In the past two decades, it has become evident that mercury compounds have various effects on the immune system. In previous reports in this series [10–13] we have considered various approaches to assessing exposures to different sensitizing metals, including the lymphocyte transformation test (LTT) [11], cytokine profiling [12], and determination of lymphocyte subpopulations [13]. This report focuses on mercury. The immunotoxic effects of mercury are more complex than those of most other metals [14]. Depending on animal species and experimental conditions, mercury compounds may cause immunosuppression or immunostimulation, autoimmune reactions, or hypersensitivity. Here we survey the immune effects of mercury and discuss the current status of risk assessment and diagnostic tests for immune effects of mercury in humans.

FATE OF MERCURY COMPOUNDS IN THE LIVING ORGANISM

When dealing with the effects of mercury in the living organism, it is important to keep in mind that different species of mercury are absorbed, distributed, and metabolized in specific ways. For instance, metallic mercury vapor is readily taken up by inhalation, then rapidly oxidized by enzymes to more reactive Hg^{2+} species, which bind to macromolecules and then tend to have a long half-life in the body.

The final distribution among organs is influenced by metal-binding proteins, notably the metallothioneins [15], other sulfur-rich proteins, and selenoprotein P. Uptake of mercury by inhalation is the most common route of exposure in the work place, but may also occur at home, e.g., in the case of a broken mercury thermometer. Uptake of mercury from dental amalgam also occurs mainly by the inhalational route [16]. Metallic mercury in skin-lightening creams can be taken up by inhalation and may lead to intoxications [17]. On the other hand, lipophilic methylmercury, which is biomagnified in fish, is readily absorbed in the intestine after fish meals. Methylmercury is accumulated in the brain, where it exerts its neurotoxic effects, but some of the compound is demethylated to inorganic mercury species [14]. Dermal uptake prevails for the wound antiseptic mercurochrome, and uptake from tissues occurs when thimerosal (merthiolate, thiomersal) [ethyl(2-mercaptobenzoato-(2)-O,S)mercurate(1-) sodium], which has been widely used as a vaccine stabilizer, is injected with the vaccine.

The toxic effects of most mercury compounds are believed to be due to the high reactivity of many mercury species toward thiol-groups and other functional groups, notably in proteins. Cross-reaction between functional groups and conformational changes may occur. Although other metals can share this type of reactivity, mercury seems to exhibit the most diverse effects on the immune system among metals, making it attractive as a model substance to study interactions between metals and the immune system. Some aspects of these interactions have been described in earlier reviews [14,18–21].

TYPES OF IMMUNOTOXICITY RESPONSES

In contrast to other organs, the immune system is not confined to a specific anatomic location. Its major locations are the bone marrow, lymphatic organs (e.g., lymph nodes, thymus) and blood, but cells of the immune system are active in virtually all organs. Many groups of chemicals are known to have an effect on the immune system [22,23]. When chemicals are tested for immunotoxicity, structural parameters may be used, such as mass of the lymphatic organs, histology of the bone marrow, and amount of circulating immunoglobulins, but measurement of changes of functionality of the immune response are just as important [24,25].

The immune system can respond to the immunotoxic effect of a substance either by immunosuppression or by immunostimulation (Fig. 1). Immunosuppression is a depression of components of the immune system with the consequence of a decreased immune response. The opposite effect, immunostimulation, can happen in different ways: First, an unspecific immunomodulation response may occur, resulting in an increased functionality of the immune system toward antigens, including those associated with infections or cancer. This latter mechanism can play a role in therapy, but is of less importance in immunotoxicology. Second, an autoimmune response may arise, when the immune system starts to lose its tolerance toward self-molecules and attacks structures of the organism. Substance-specific sets of autoantibodies are formed and substance-specific organs are damaged. Third, a hypersensitivity response may occur, when the immune system becomes sensitized to a substance (often as a hapten) and results in an allergic reaction.

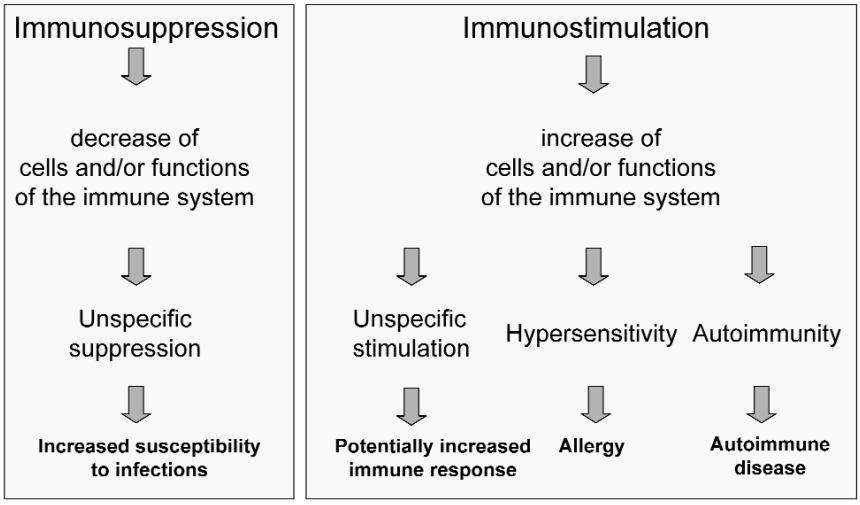

Fig. 1 Some possible effects of metals on the immune system. The scheme shows the various types of immunotoxic effects of some metals (such as mercury, nickel, and gold) and other chemical compounds, and the respective clinical consequences. Mercury compounds can induce each of these effects under appropriate conditions. There is much overlap between stimulation, suppression, hypersensitivity, and autoimmunity.

FINDINGS IN RODENTS

Mercury-sensitive animal strains

There are three inbred strains of rat that are mercury-sensitive, whereas 17 other strains can be considered as mercury-resistant [26]. Most studies have been done with the sensitive Brown Norway rat or with sensitive mouse strains, and a few studies with sensitive rabbits [14]. Mercury-insensitive strains often serve as controls or to study nonspecific effects.

Immunosuppression and immunostimulation in rodents

Injection of mercury(II) chloride in mercury-insensitive strains of laboratory animals (e.g., the Lewis rat) causes an immunosuppression, and leads to a reduced reactivity of cells of the immune system [27]. Immunosuppression is also a feature of methylmercury poisoning, and some authors have evidence from studies in susceptible mice that the immune system is as sensitive as the brain [28]. Immunosuppression does not exclude the possibility that in a later phase immunostimulation may occur [28]. Immunosuppression can lead to a decreased immunological defense against infectious agents [29]. Thus, pretreatment of mice with mercury compounds enhances susceptibility to experimental infections with murine leishmaniasis [30] or sporozoites [31].

When mercury is given to mercury-sensitive rodent strains, an increased reactivity of the immune system (i.e., immunostimulation) can be observed. Mercury-susceptible Brown Norway rats were given silver-amalgam restorations in four molars (250–375 mg Hg/kg body mass). They showed an up to 12-fold increase of IgE-antibodies and increased titers of immune complexes in the renal glomeruli [32], whereas non-mercury-susceptible rat strains did not show such an effect. T-lymphocytes from donor mice treated for a week with subcutaneous injections of mercury(II) chloride were tested in a popliteal lymph node assay. Cells mounted a response to mercury(II) chloride and to splenic proteins isolated from mercury-treated mice [33]. The latter proteins contained mercury. Mercury salts have been shown to affect cytokine production by triggering Ca^{2+} signals and activating protein kinase C [34]. Mouse strains either sensitive or resistant to mercury were given an oral challenge of mercury(II)

nitrate [35]. Increased mRNA expression of IL-2, IL-4, and IFN-γ occurred in the lymphoid tissue of sensitive mice, whereas IL-10 expression was increased and IL-2 and IFN-γ expression were decreased in the resistant mice. The changes in cytokine production reflect changes in T-cell populations, and mercury(II) chloride has been proposed to cause immune dysfunction by favoring activation of TH2 cells over TH1 lymphocytes [36]. Some of these immunostimulatory effects are related to autoimmune effects.

Autoimmunity in mercury-sensitive rodent strains

Mercury causes autoimmunity in some strains of rats, mice, and rabbits [14]. Mercury(II) chloride induces anti-glomerular basement membrane antibodies in the Brown Norway rat. Various other inbred rat strains (Lewis, Wistar AG, August, PVG/c) do not produce such antibodies under the same experimental conditions [37]. The immune reaction in mercury-sensitive Brown Norway rats is accompanied by an autoimmune renal disorder, identified as a membranous glomerulonephropathy [14,38,39]. After inhalation of mercury vapor (0.3–1.0 mg Hg/m^3 air for up to 10 weeks), mercury-susceptible mouse strains produce antinuclear antibodies, followed by deposition of immunocomplexes in the glomerulus [40]. The lowest effective dose for formation of antinuclear IgG was at a calculated weekly exposure of 170 μg $(kg\ body\ mass)^{-1}$; IgG concentrations peaked after 2–4 weeks [40]. Shifts in the ratios of lymphocyte subpopulations have also been observed in rodents [41]. Although B-lymphocytes and their autoantibody-products are of major importance in the autoimmune process, there is some evidence that active T-lymphocytes, and possibly suppressor-cells, are also involved [33,42–44].

Mercury-induced autoimmunity in genetically susceptible strains is characterized by T-cell-induced polyclonal B-cell activation, increased levels of IgE and IgG1, production of autoantibodies to laminin, polyclonal production of antinuclear antibodies, and systemic deposits of immunocomplexes, especially in the renal vessels [45–48]. The biochemical pathomechanisms may include a B-cell-activating agent which belongs to the family of tumor necrosis factors [49], and disturbed signal transduction at the T-cell-receptor (TCR) [50] as well as T-cells and Fc-receptors [45]. When mercury-sensitive newborns are treated with mercury(II) chloride, they become mercury-resistant [51]. This might be caused by a CD8-T-cell-mediated reaction [52].

An autoimmune-like profile with increased anti-nuclear antibodies has been observed after treating mice with mercury(II) salts [53]. Many of the autoantibodies are reactive with fibrillarin, a nuclear ribonucleoprotein that may be targeted in some scleroderma patients [54–56]. Antibodies to laminin are a common finding in experimental mercury exposure [57]. Laminin is a glycoprotein in the extracellular matrix and important for the anchoring of cells. Activation of CD4+ Th2 cells has also been reported, with release of IL-4 and increased IgE production [58,59]; a neutralizing anti-IL-4 antibody prevented a rise in IgE in mice treated with mercury(II) chloride [53]. Some of the parameters known to be involved in the autoimmune response are shown in Fig. 2.

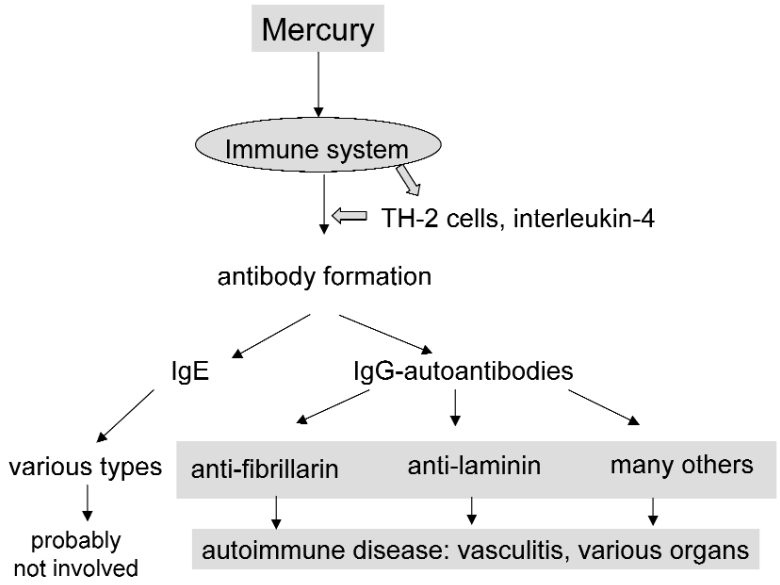

Fig. 2 Important steps of mercury-induced autoimmunity. The scheme shows some of the most common findings with oral and parenteral exposure to mercury(II) salts, but experiments in mercury-sensitive rats and other rodents have elucidated many more details of the mechanisms (see text). TH-2 cells = TH2-helper cells, IgE = immunoglobulin E, IgG = immunoglobulin G.

Autoimmunity has an unusual time course in sensitive rats and mice [60–62]. The maximum level of antibodies is reached after about two weeks. Even when mercury treatment is continued, the B-cell activation and the titers of autoantibodies decrease thereafter. This seems not to be due to an immunosuppression [63].

Apoptosis, or programmed cell death, is an essential process that destroys self-recognizing lymphocytes during their maturation process. Various studies have shown that mercury influences apoptosis in lymphocytes, and this might disturb the normal lymphocyte selection process. Increased apoptosis [64], as well as attenuated apoptosis [65,66] have been observed. One idea is that such effects on apoptosis might allow self-recognizing lymphocytes to survive.

Altogether, many experimental approaches have been used to study mercury-induced autoimmunity, including chimeric animals [67], antibodies against surface molecules of lymphocyte subsets [68], and genetic approaches [69]. However, the mechanisms initiating autoimmunity are still unclear. One may suppose that the primary event is the binding of mercury to a major histocompatibility antigen (MHC)-molecule, to a TCR or to a processed self-peptide [23,58]. The scheme in Fig. 3 is a hypothetical model, depicting some of the possibilities.

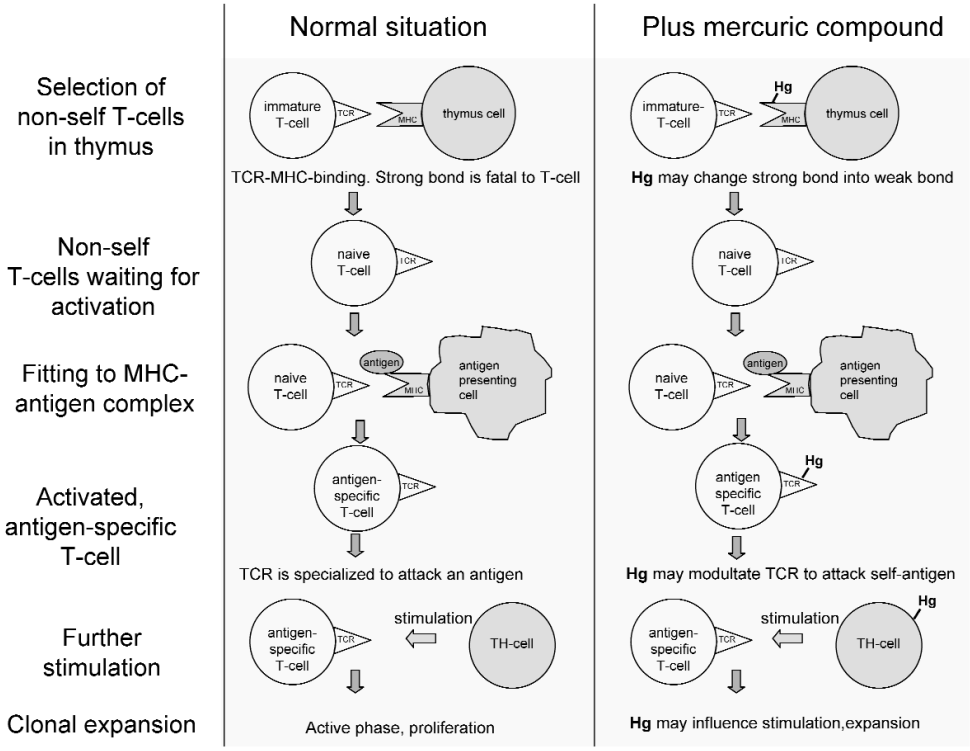

Fig. 3 Primary targets that might lead to autoimmunity. The scheme shows some steps in the lifetime of a lymphocyte, in which mercury binding to proteins/peptides might result in adducts, that support the attack of "self-proteins". The left panel ("normal situation") depicts important steps of normal maturation and activation of lymphocytes. The right panel ("plus mercuric compound") shows some possibilities of how mercury binding to proteins or peptides might change them in such a way that lymphocytes will be directed against self-molecules. MHC-molecules are located on each cell, notably on cells of the thymus, which induce death of maturing lymphocytes that have too strong an affinity to MHC-cells. The MHC-molecules on antigen-presenting cells (APCs), such as dendritic cells, bind degraded protein-fragments and present them to the TCR of T-lymphocytes. TCR = T-cell receptor, the antigen-detecting entity of the T-cell. MHC = major histocompatibility antigens. TH-cell = T-helper cell.

Autoimmunity in nonsensitive rodent strains

Even rodent strains which are not considered to be specifically mercury-susceptible, may under certain circumstances become responsive to mercury [70,71]. Thus, a 14-day pretreatment with $HgCl_2$ [two weeks of 20–200 μg mercury (kg body mass)$^{-1}$, subcutaneous, every second day] followed by an experimental induction of a lupus-like-disease, caused an increase in lupus-like symptoms in nonsusceptible mouse strains [72]. The authors concluded that mercury may act as a cofactor, which favors autoimmune disease when combined with other factors, such as genetic disposition or certain infectious disease [71]. Paradoxically, mercury counterregulated the spontaneous autoimmune diabetes in nonobese diabetic mice [46].

Hypersensitivity in laboratory animals

Allergic contact dermatitis can be induced by mercury in a BALB strain of mice [73] and in Brown Norway rats [74]. Aspects of the cellular mechanism of mercury contact sensitivity were studied in mice [75]. It was difficult to produce contact dermatitis in the oral mucosa of the rat [76]. Rats received

local exposure of the right buccal mucosa, either to amalgam or to an alloy free of mercury. After 20 days, more than 90 % of the animals showed changes of the adjacent mucosa (oral lichenoid reactions), which meant that mercury appeared to be irrelevant for this type of change [77].

Occular hypersensitivity to thiomersal is strong and related to thiomersal-specific antibodies in tears and serum [78]. Immunization of rabbits with thimerosal that was chemically coupled to proteins resulted in the production of antibodies which specifically reacted with thimerosal, with a high potential to cause occular hypersensitivity [79]. Thimerosal also spontaneously reacted with proteins [79].

FINDINGS IN HUMANS

Studies in humans

Many observations on the effects of mercury in humans come from studies in occupational medicine. In former years, workers in mercury-specific work places were often exposed to high concentrations of mercury vapor, which considerably exceeded the exposure of the general population. However, because there is now much concern about possible chronic health effects of low-level mercury exposures, studies of people with low exposures are now also being undertaken.

Immunostimulation and immunosuppression in humans

Lymphocyte markers of mercury exposure have not been demonstrated consistently. Transiently increased exposure during removal of amalgam fillings appears to have no effect on CD4+, CD8+ or B-cells [80], whereas exposure to metallic mercury fumes caused an increase in CD4+ and CD8+ cells [81]. However, another study observed a decrease of CD4+ cells and NK-cells [82], and an inverse (though not statistically significant) relation between urinary mercury concentration and NK-cells was found by others [83]. Mercury suppresses T-cell activation in vitro [84], especially if the cells have a low glutathione content [85]. Both organic and inorganic mercury compounds induce apoptosis in human lymphocytes [65,86,87].

Autoimmunity in humans

Autoimmune reactions are the basis of many chronic diseases such as rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosis, scleroderma, and Hashimoto's disease. As mercury has a potential to induce autoimmunity in animals, it is of interest to determine whether mercury may induce or exacerbate autoimmune disease in humans. In this context, two mercury compounds have been very controversial in the past few years. These are amalgam, the dental restoration material, and thiomersal, an ethylmercury-containing organic compound which has been widely used in vaccines, but has been mostly replaced in recent years.

Swedish authors came to the conclusion that there may be a health hazard of mercury, more precisely of amalgam and its effects on the immune system [88]. Others did not find evidence for such an effect of mercury [89–93], even at higher dosage [94], and found no correlation with acute autoimmune disease such as acute glomerulonephritis or childhood purpura [95]. An epidemiological analysis found a weak association with lupus erythematosus, but this remains to be further investigated [96]. When lymphocytes of patients with autoimmune thyroiditis were incubated in vitro with mercury salts, there was a trend for an increased production of antibodies [97]. Workers who had been occupationally exposed showed an inverse relationship between exposure to metallic mercury (mean concentration in the urine 45 $\mu g\ L^{-1}$) and the number of activated T-lymphocytes [82].

Many pathologic processes in the brain are accompanied by local inflammatory events [98]. Some authors have assumed that amalgam might favor such processes. In a study in the United Kingdom, there was no correlation between the number of amalgam fillings and multiple sclerosis, but an in-

creased rate of dental caries was found in patients with multiple sclerosis [99]. Similar results were found in an Italian study [100]. In a Canadian study on the relationship between amalgam and multiple sclerosis, persons with more than 15 amalgam fillings showed a higher disease rate, but this was not statistically significant [101]. It has been proposed that autism might be associated with autoimmune processes. Various potential triggers for such an autoimmunity have recently been discussed, such as viral infections and exposure to thiomersal [102–104]. However, there are experimental findings that contradict the involvement of thiomersal [105–107]. The question whether mercury might be involved in the formation of antisperm antibodies that cause reduced fertility, has been studied. Results so far are controversial [108,109].

In a Czech study, 25 out of 35 patients reported improvement of their chronic autoimmune diseases (systemic lupus, multiple sclerosis, autoimmune-thyroiditis) and allergies after removal of their amalgam fillings [110]. However, this study gives little exact information about the improvement of symptoms. In a study in Germany, the body burden of mercury was associated with acute atopic eczema and total IgE in children [111]. An association with pemphigus, an autoimmune skin disorder, was seen in an area in Columbia which is contaminated with mercury [112].

An analysis of the literature in occupational medicine did not reveal consistent relationships between exposure to mercury vapor and the function of the immune system [113]. Likewise, another review found little evidence for a relationship between amalgam and autoimmune disease [114]. An investigation of workers occupationally exposed to mercury reached the conclusion that mercury-induced autoimmunity—if it exists at all in humans—must be very rare [94]. In conclusion, the present information suggests that the risk of a mercury-related autoimmune response in humans is very low, since even more highly exposed workers did not show any reproducible relationships.

Estimation of risk for autoimmune reactions in humans

In order to get further information on the potential risk, we estimated the safety margin between the dose that causes an autoimmune effect in experimental animals and the typical mercury exposure of humans in many countries. The first autoimmune responses were seen in rodents at a dose of about 50 μg mercury (kg body mass)$^{-1}$ (day)$^{-1}$ [72]. In a study with genetically mercury-susceptible mice, the threshold weekly dose for formation of antinuclear IgG was at 170 μg (kg body mass)$^{-1}$, or about 20 μg (kg body mass)$^{-1}$ (day)$^{-1}$, for 10 weeks [40]. Mercury absorption from dental amalgams typically amounts to less than 0.02 μg (kg body mass)$^{-1}$ (day)$^{-1}$ [16]. Thus, the weight-adjusted dose required to cause an autoimmune effect in mercury-susceptible rodents is about 1000-fold higher than the mercury dose typically taken up by humans. It remains unclear whether there are mercury-sensitive individuals in the human population, for whom the margin of safety might be smaller.

Hypersensitivity in humans

Contact with mercury salts such as the chloride and amide chloride may cause hypersensitivity [115]. Symptoms include changes of the skin and mucous membranes, such as eczematous dermatitis or stomatitis [116,117]. In a Japanese study, 13 % of the volunteers were sensitized to mercury as detected by the patch test. There was an association with the content of mercury in hair of the volunteers, but not in urine [118]. In a study with 2776 consecutive patients, 13.2 % were positive to ethylmercury(II) chloride, 11.8 % to thimerosal, and 8.9 % to metallic mercury [119]. Hypersensitivity was also described after dermal application of mercurochrome [120,121] and in connection with mercury in tattoos [122]. However, occupational contact dermatitis from mercury is considered to be rare [20], and a positive patch test for mercury is generally without clinical consequences [115]. Amalgam can induce allergic reactions in humans in rare cases [123]. These alterations of the oral mucosa (lichen planus or lichenoid reaction) may be located at the sites of contact with amalgam [124]. Studies with biopsies showed increased mercury levels in the adjacent tissue and increased counts of mononuclear cells. These in-

creased cell counts are believed to be associated with a type 4 allergic reaction in some patients and with an unspecific reaction of the immune system in others [125–127]. When amalgam is removed, the alterations of the oral mucous membranes are usually reversible [128–131].

Tests for hypersensitivity in humans

Like nickel, cobalt, and some other metals, mercury can induce a type 4 allergic reaction, although the occurrence of mercury allergies in humans is far lower than for some other metals. Type 4 allergic reactions involve T-lymphocytes. Standard procedures to detect type 4 allergens can be performed on the skin of the patient (patch test or skin test) or on T-lymphocytes that have been isolated from the blood of the patient (LTT).

Patch test: If a patient is suspected of having a mercury allergy or a lichen planus of the mouth, further clarification can be done with the patch test [120,128,132,133]. Like many other tests in allergology, this test has only a limited sensitivity and specificity.

Lymphocyte transformation test (LTT): Variants of this test are called lymphocyte proliferation test (LPT) or lymphocyte stimulation test (LST). The principle of the test is based on the fact that lymphocytes which are sensitized with a certain antigen (i.e., they are memory cells), are induced to become blasts after a new contact with this antigen. The LTT is used to detect specific sensitization of patients toward foreign antigens (infectious agents, allergens) or autoantigens (autoimmune diseases). Several studies have evaluated the LTT for mercury [134–137]. The test was optimized to demonstrate a higher incidence of lymphocyte reactivity to mercury in patients with amalgams, with or without oral lichen planus, compared to controls without amalgams [134]. However, on further evaluation, the test did not reliably distinguish volunteers with or without amalgams, nor those with oral lesions and a positive patch test to mercury(II) oxide [134]. In fact, sensitivity was only 33–67 % and specificity was 0–70 %. The LTT with mercury shows a high rate of positive results in healthy people with or without amalgam [135,138], and does not appear to be very useful for detecting mercury sensitization or for distinguishing whether the patient's condition is caused by mercury exposure [11].

The memory lymphocyte immunostimulation assay (MELISA) is a patented test used by some laboratories [134]. The name is somewhat misleading, because it suggests that the test is based on an enzyme-linked immunoabsorbent assay (ELISA) principle when it is, in fact, a modified LTT. The modifications are as follows [138]: the plates are pretreated with the mercury compound, monocytes are removed from the sample, a higher cell count of lymphocytes is used, lower mercury concentrations are employed (in order to minimize unspecific stimulation of lymphocytes by mercury), and the commonly measured incorporation of [^{3}H]-thymidine into DNA is complemented by a morphological control. It has been proposed that these modifications make the test superior to a common LTT. However, this is not necessarily so. For instance, as reported [138] the monocytes are only partially removed, the number of lymphocytes employed is in fact smaller than in the LTT of many laboratories (1 million instead of 3 million), the range of mercury concentrations used is smaller than in many other labs, and finally, many other labs also use supplementary parameters to study the state and viability of the lymphocytes.

There are several positive reports of the suitability of the MELISA test for mercury sensitization [109,110,134,139–141]. In most of these publications, adequate control groups are missing and an objective evaluation of the test is not possible. In other studies that include control groups, the test is generally not considered to be useful [135]. In patients with dental amalgam-related contact lesions, there was no evidence for specific LTT reactivity [142]. In principle, the MELISA should be considered a LTT. It has not been adequately demonstrated to be useful in the diagnosis of metal allergy [143].

A positive LTT or MELISA suggests that a person has lymphocytes which are sensitized to mercury. Results are often false-positive, and this may have unwanted consequences for the patient. The detection of sensitized lymphocytes does not correlate with an effector reaction (clinical manifestation), and the relationship with a mercury allergy or susceptibility is not sufficiently supported by the literature.

DEVELOPMENT OF RESISTANCE

Bacterial mercury resistance is a well known phenomenon, which may be related to reductase enzymes that convert mercury(II) species to volatile metallic mercury [144]. Although development of bacterial resistance is not an immunological event, it may well have immunological consequences. It was observed that bacteria in the oral cavity developed a mercury resistance which is transferred on the same plasmids as some antibiotic-resistances. Therefore, it was postulated that continuous mercury exposure might cause a continuous selection pressure toward an antibiotic-resistant state [145]. Mouth flora of some children also contain bacteria resistant to mercury and to antibiotics [146]. However, others found that amalgam fillings in children had hardly any influence on resistance of mouth bacteria toward mercury or antibiotics [147,148].

CONCLUSIONS

Mercury has profound immunological effects in laboratory animals at comparatively low doses. It has, therefore, become a model metal that is used to study mechanisms of autoimmunity. However, the situation is complex. Depending on mercury speciation and experimental conditions, mercury not only induces hypersensitization and aggrevates autoimmunity, but in some instances may also elicite immunoprotection. Mercury hypersensitivity in humans can be tested with some reliability with the patch test, and with lower reliability in the LTT. However, there is no reliable way to test whether an autoimmune disease of a patient is related to mercury. Mercury used to be a widely applied industrial and pharmaceutical chemical, which often led to high exposures and overt toxicity in humans. Due to the ongoing restrictions in usage of mercury compounds, the former high exposures are extremely rare today in many countries. Nevertheless, the debate continues over whether there are specifically sensitive people, in whom the present mercury exposures might be sufficient to disturb the immune system.

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