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Review

Mercury and autoimmunity: implications for occupational and environmental health

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Abstract

Mercury (Hg) has long been recognized as a neurotoxicant; however, recent work in animal models has implicated Hg as an immunotoxicant. In particular, Hg has been shown to induce autoimmune disease in susceptible animals with effects including overproduction of specific autoantibodies and pathophysiologic signs of lupus-like disease. However, these effects are only observed at high doses of Hg that are above the levels to which humans would be exposed through contaminated fish consumption. While there is presently no evidence to suggest that Hg induces frank autoimmune disease in humans, a recent epidemiological study has demonstrated a link between occupational Hg exposure and lupus.

In our studies, we have tested the hypothesis that Hg does not cause autoimmune disease directly, but rather that it may interact with triggering events, such as genetic predisposition, exposure to antigens, or infection, to exacerbate disease. Treatment of mice that are not susceptible to Hg-induced autoimmune disease with very low doses and short term exposures of inorganic Hg (20–200 μg/kg) exacerbates disease and accelerates mortality in the graft versus host disease model of chronic lupus in C57Bl/6 × DBA/2 mice. Furthermore, low dose Hg exposure increases the severity and prevalence of experimental autoimmune myocarditis (induced by immunization with cardiac myosin peptide in adjuvant) in A/J mice. To test our hypothesis further, we examined sera from Amazonian populations exposed to Hg through small-scale gold mining, with and without current or past malaria infection. We found significantly increased prevalence of antinuclear and antinucleolar antibodies and a positive interaction between Hg and malaria. These results suggest a new model for Hg immunotoxicity, as a co-factor in autoimmune disease, increasing the risks and severity of clinical disease in the presence of other triggering events, either genetic or acquired.

Keywords: Mercury; Autoimmune dysfunction

Contents

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Introduction

Exposures to mercury (Hg) compounds continue to be prevalent and significant health risks to both workers and nonoccupational populations (Gochfeld, 2003). In addition, mercury is recognized as a global pollutant, primarily associated with exposures to methyl mercury (MeHg) via fish consumption (Damstra, 2002; Cohen et al., 2004; NRC, 2000). These exposures, although outside the scope of this review, emanate largely from fossil fuel burning (EPA, 1997; Meij et al., 2002) and because of their extent must be considered as a "background" for the total exposures of working populations. Recent studies by the US Centers for Disease Control and the Environmental Protection Agency have estimated, on the basis of population-based sampling, that over 500,000 US women of childbearing age have blood Hg levels in the range of concern for potential adverse health effects for the developing fetus (Schober et al., 2003; Mahaffey et al., 2004).

Current sources of occupational exposure to Hg vary worldwide. They involve elemental Hg, organomercurials, and inorganic Hg (iHg) compounds (EPA, 1997; WHO, 1991). Elemental Hg is used in thermometers, thermostats, and other gauges, as well as in a range of electrical switches and devices and as ballast in fluorescent lights. In addition, elemental Hg has been measured in workplaces where inorganic Hg is used (Potter, 2002) and spills of liquid elemental Hg constitute significant, specific exposures in the workplace (Zeitz et al., 2002). Elemental mercury is also used in the preparation of amalgams for dentistry with documented exposures to dental personnel and patients (NRC, 2000). In developing countries, elemental Hg is still used in amalgamation processes for gold extraction in small-scale gold mining; this use contributes a significant portion of the global anthropogenic Hg budget (Lacerda et al., 2004; Lodenius and Malm, 1998). Other Hg exposures can occur in mining, such as when Hg occurs as a contaminant in copper and gold ores. In many countries, alkyl and phenyl mercurials are used in paints and pesticides (WHO, 1991). In the chemical industry, Hg catalysts are used in chloralkali and chlorine production. Because of the extensive use of Hg in consumer products, occupational exposures can occur in handling and processing a variety of wastes and waste residues (municipal and industrial solid wastes as well as biosolids) (van Veizen et al., 2002; WHO, 1991; EPA, 1997). For example, it has been estimated that discarded fluorescent light bulbs alone may release 2–4 tons of Hg per year in the US (Aucott et al., 2003). Pollution control technologies, such as scrubbers that strip Hg from air emissions, result in concentrations of Hg in various forms, requiring additional management.

Mercury compounds are considered highly toxic largely for effects on the nervous system, kidney, and skin; in addition, inhalation of mercury can cause devastating acute toxicity to the lung (NRC, 2000; Clarkson et al., 2003). Public health concerns have focused on developmental neurotoxicity, associated with prenatal exposures to MeHg, as the critical endpoint of concern for national and international policies to prevent exposure and reduce anthropogenic emissions (reviewed by Clarkson, 1997; Mahaffey, 2000; NRC, 2000). This conclusion is based upon extensive review of epidemiological data from the Faeroes (Grandjean et al., 1997) and the Seychelles (Myers et al., 1997), as well as from experimental studies (recent reviews by Faustman et al., 2002; Rice and Barone, 2000; Mahaffey, 2000). The fetus has been considered to be "specially susceptible" to MeHg, but this has been questioned by some recent studies reporting that adults may be as sensitive to the neurotoxic effects of Hg compounds as are children (Iregren et al., 2002; Yokoo et al., 2003; Beuter and Edwards, 2004).

Hg and the immune system

The extensive epidemiological and experimental literature on mercury, and the clear definition of risks to children might suggest that further consideration of mechanisms of mercury toxicity is not necessary. However, as discussed in this review, the possible immunotoxic effects of mercury compounds have not been considered in assessing the risks of Hg exposures. These endpoints may significantly raise new health concerns, in terms of identifying significant interactions with other risk factors and potentially susceptible populations. Several recent reviews of MeHg risks have identified immunotoxicity as a critical area of further research (EPA, 1997, NRC, 2000). Concerns over the immunotoxic manifestations of Hg exposures have been most recently raised in connection with use of Hg in dental amalgams and the use of ethyl Hg (thimerosal) as a preservative in some vaccines (NRC, 2000). While considerable controversy exists about the health significance of these two exposure sources, it is clear that both dental amalgams and thimerosal containing vaccines can result in increased levels of Hg in exposed persons (Ely, 2001; Havarinasab et al., 2004).

The immunotoxic hazards of Hg compounds have been extensively demonstrated in animal models, to include both autoimmune dysfunction and immunosuppression. The *autoimmune* effects of Hg in susceptible rodent strains include signs of systemic and organ-specific pathology (both renal and vascular), induction of specific autoanti-

bodies and autoreactive T cells, polyclonal activation of T and B cells, increased serum IgG1 and IgE, cytokine dysregulation and an immune complex-mediated glomerulonephritis (for reviews, see Bigazzi, 1994, Griem and Gleichmann, 1995; Lawrence and McCabe, 2002; Hultman and Hansson-Georgiadis, 1999). Despite this extensive literature, the human health significance of these extensive experimental findings is unclear since autoimmune manifestations are seen only in certain inbred strains of rats and mice and most studies have been conducted at relatively high doses. In contrast to the strong concordance between experimental and epidemiological studies on MeHg-induced neurodevelopmental toxicity (Burbacher et al., 1990; Rice and Barone, 2000), there is substantial uncertainty about whether there are immunotoxic risks to humans associated with environmental or occupational exposures to Hg compounds (see Moszczynski, 1999, and Sweet and Zelikoff, 2001 for reviews). No associations have been found between Hg exposure and any clinically defined autoimmune disease in humans, even in highly exposed workers. A study of workers reported that levels of circulating anti-laminin antibodies were increased in chloralkali workers, as well as autoantibodies against glomerular basement membrane proteins and circulating immune complexes (Lauwerys et al., 1983). However, overall, studies of lymphocyte subsets or immunoglobulin levels in occupationally exposed cohorts are inconsistent (e.g., Moszczynski et al., 1996; Vimercati et al., 2001; Soleo et al., 1997; Dantas and Queiroz, 1997; Barregard et al., 1997; Aymaz et al., 2001). Most interestingly, a recent small case-control study reported an association between increased levels of urinary Hg and odds of more severe scleroderma, accompanied by elevated urinary creatinine and serum antifibrillarin autoantibodies (Arnett et al., 2000). However, the levels of urine Hg in all persons in this study were quite low and it is not possible to exclude reverse causation, since disease-related alterations in renal function could have increased the urinary excretion of Hg.

Nevertheless, it cannot at present be concluded that humans are resistant to Hg-induced immunotoxicity. The discrepancies between findings in experimental and epidemiological studies are more apparent than real: first, the animal studies have almost exclusively used females, while there is very little information on women and children; second, there are very few studies of immune function in persons exposed to MeHg; and third, the methods used to investigate immune function in Hg-exposed humans are not as sensitive or specific as those that have been used to evaluate neurodevelopmental and/or neuropsychological endpoints in Hg-exposed children and adults.

Moreover, it has been suggested that immunologic mechanisms may be involved in nephropathy and neurotoxicity, two well described toxic effects of Hg in workers. The nephrotoxic effects of Hg, which have been reported in workers with either acute or chronic exposures to Hg, may involve deposition of autoantibodies to glomerular basement membrane proteins (Moszczynski, 1999; Druet, 1989; Langworth et al., 1992). The neurotoxic effects of mercury may also involve immunologic effects. Recently we suggested that immunologic mechanisms may also be involved in Hg-induced developmental neurotoxicity, which is characterized by inhibition of neuronal migration in both humans and experimental models (Sass et al., 2001). We showed that Hg inhibits neuronal migration through disrupting cytokine-directed intercellular communication between neurons and microglia (Calderon-Aranda et al., 2004). Similar effects were recently reported by Hornig et al. (2004). The developing nervous system and the immune system are in many ways conceptually and biologically linked: neuronal migration involves intercellular interactions that utilize the same signaling molecules as the immune system (cytokines and chemokines, among other signaling molecules). Appropriately timed and accurately directed neuronal migration (both radial and tangential) is essential to the formation of the mature CNS. Microglia, cells that perform important roles in neuronal migration, are cells of macrophage lineage that synthesize, release, and respond to immunologic signals. They function in the mature CNS to respond to infection and cell injury. However, there is a specific role for these signals during neurodevelopment as trophic factors, specific to a defined period in CNS development. With respect to neurotoxic outcomes in adults, the continuing contribution of neurons from the stem cell pool to regions of the adult brain requires the same mechanisms of glial–neuronal interactions in neuronal migration for progenitor cells to move from germinal zones to anterior/posterior positions in the CNS (Hatten, 2002; Marin and Rubenstein, 2003) Thus, through this mechanism exposures to Hg at any stage in life may contribute to neurodegenerative disease by depleting the supply of potential cellular replacements (Lie et al., 2004).

The dysregulation/trigger hypothesis of Hg immunotoxicity

In this paper, we review the data associating occupational and environmental Hg exposures with autoimmune dysfunction, as distinct from autoimmune disease. This distinction is important, since we hypothesize that Hg compounds contribute to the induction and/or severity of autoimmune disease by dysregulating cellular and molecular responses to triggering events. Our hypothesis is shown schematically in Fig. 1. In this model, the role of Hg in the expression of autoimmune disease depends upon co-exposures to other risk factors, such as genetic predisposition, infection, or antigen exposure. Hg may interact by “resetting” the immunologic milieu such that host responses to a triggering event are altered, or Hg may amplify the effects of a triggering event. Our hypotheses have been developed from new data, by our group and others, using experimental

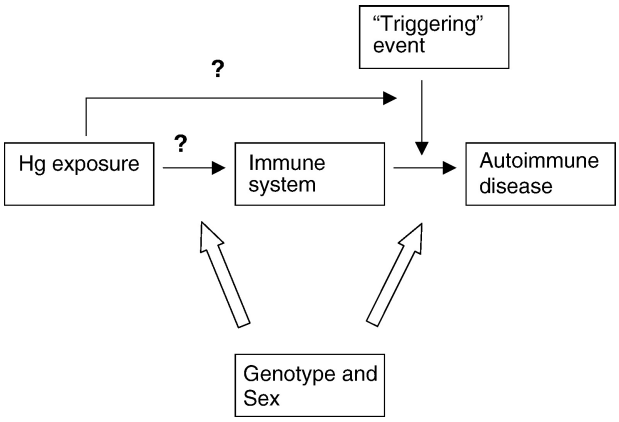

Fig. 1. Schematic representation of possible interactions between Hg exposure and immune function in autoimmunity. As depicted, there are at least two potential mechanisms by which Hg may be associated with increased risks of autoimmune disease: Hg may affect the response pathways of the immune system, within the milieu of genotype and sex, such that subsequent responses to a "trigger" (infection, antigen, or organ damage) lead to autoimmune disease. Alternatively, Hg may affect the response of the immune system to a "trigger" through immunosuppression, T- or B-cell activation, or enhancing organ damage.

designs that examine interactions between low levels of Hg exposure and triggers (intrinsic or acquired) of autoimmune disease. Based upon these results, we have examined biomarkers of autoimmune dysfunction in populations exposed occupationally and environmentally to Hg compounds.

The interactions among factors involved in autoimmune disease may be generally conceived in terms of interactions among triggering events and pre-existing susceptibility to autoimmune disease (Powell et al., 1999; Via et al., 2003; Fournie et al., 2001). Susceptibility may be either intrinsic or acquired (Rose, 2002). We propose that Hg can alter responses to events that induce autoimmunity by interacting with the immunologic milieu of individuals, which may be shaped by either genotype, endogenous hormones, or acquired risk factors that influence the modes of immunologic response (such as Th2 skewing).

Hg as a risk factor for autoimmune disease fits the conceptual model of complex gene–environment interactions proposed for autoimmune disease (Cooper et al., 1999; Rose, 2002). For this model, Hg is one of the strongest candidates for a preventable cofactor in the induction or exacerbation of autoimmune diseases (Powell et al., 1999), many of which occur with unequal prevalence or severity depending upon sex or ethnicity. In mice, there is a clear gene–environment interaction involved in iHg- and MeHg-induced autoimmune manifestations, in terms of both pathophysiology and also the specific autoantibodies produced (Pietsch et al., 1989; Warfvinge et al., 1995; Robinson et al., 1997; Hultman and Hansson-Georgiadis, 1999; Hultman and Nielsen, 2001). There are also genetic interactions determining the effects of Hg on autoimmune disease in disease-prone strains of mice. For example, in two strains of lupus-prone mice, Pollard et al. (1999, 2001) found that Hg at very low doses accelerated systemic autoimmune disease and dysfunction, including both target organ damage and humoral features of disease. Other studies of these mouse strains prone to spontaneous autoimmune disease have confirmed that iHg treatment accelerates or exacerbates the development of disease pathophysiology (Al-Balaghi et al., 1996; Abedi-Valugerdi et al., 1997). Recently, Hornig et al. (2004) reported that exposure of SJL/J mice to a DTP vaccine containing thimerosal (an organomercurial used as a preservative in pharmaceuticals) induces a range of neurotoxic sequelae, including changes in behavior, hippocampal morphology, and neurochemistry, which were not seen in other mouse strains or in this strain in the absence of Hg exposure.

Mercury exposures and autoimmune dysfunction

Animal models

We have shown that iHg can accelerate overt autoimmune disease in two murine models of acquired autoimmune disease, lupus and cardiomyopathy, even in strains of mice that are not inherently susceptible to Hg-induced autoimmune dysfunction. Most importantly, these effects are induced by very low exposures and are associated with Hg body burdens that are within the range found in human populations (Pollard et al., 2001; Barregard et al., 1999).

Graft versus host disease

In studies of Hg and GVHD, Hg significantly accelerates disease, denoted by early mortality, early onset of proteinurea and nephropathy, and increases in serum antinuclear antibodies (ANA) and anti-single strand DNA antibodies (Via et al., 2003). A 2-week exposure of both donor and host animals to low dose iHg (20 or 200 μg/kg q.o.d.) ending 1 week prior to GVHD induction can significantly accelerate the first signs of disease as well as earlier onset of severe disease and death (Fig. 2). Pathophysiologic examination of the kidney demonstrated that iHg pretreatment clearly worsened chronic lupus-like disease, rather than GVHD worsening iHg immunotoxicity.

Autoimmune myocarditis and iHg

We have utilized the same design to examine interactions of Hg with experimental autoimmune myocarditis (Nyland et al., 2004). Two models of disease induction have been tested: infection with coxsackievirus B3 (CB3) and inoculation with the inducing antigen, cardiac myosin peptide (CMP) (Fairweather et al., 2001). In the CMP model, iHg pre-treatment (200 μg/kg q.o.d. for 15 days) increased both incidence and severity of autoimmune myocarditis, as shown in Fig. 3 (Nyland et al., 2004). By itself, iHg treatment had no effect on heart pathology or weight, demonstrating that this exacerbation was clearly related to worsening of autoimmune disease, not exacerbation of Hg toxicity.

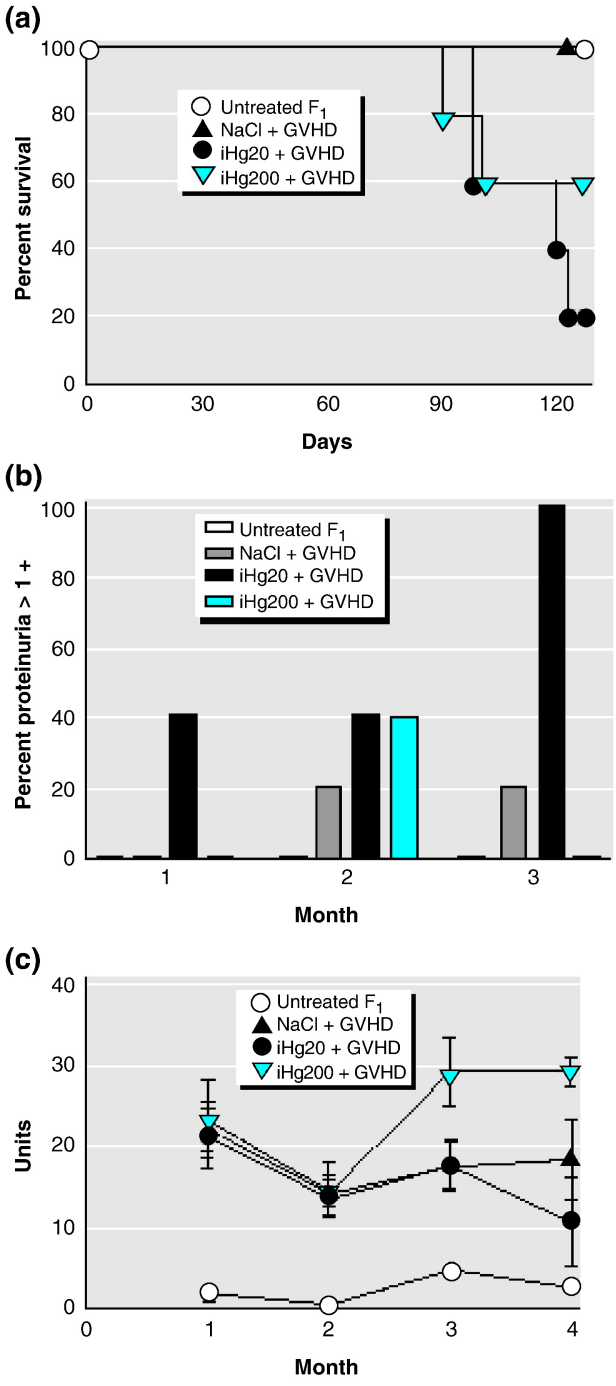

Fig. 2. Effects of Hg pretreatment (20 or 200 μg/kg q.o.d. for 15 days) of both donor and host mice, on lupus-like disease in the D2B6 F_1 model of GVHD. (a) Effects on survival; (b) effects on proteinuria; (c) effects on serum levels of anti-SS DNA. Figure reprint from Via et al., 2003.

Autoimmune dysfunction in human populations exposed to Hg

Based upon these studies, we have tested the hypothesis that Hg exposures may induce biomarkers of autoimmune dysfunction in human populations. We selected more specific markers of autoimmune dysfunction, in contrast to the studies reviewed above that have mainly measured parameters such as IgG or IgE. For this purpose, we selected antinuclear (ANA) and antinucleolar (ANoA) autoantibodies because their induction is characteristic of the autoantibody response in mice exposed to Hg (Hultman and Pollard, 1996, Robinson et al., 1997). These studies were carried out in Brazil, in collaboration with the Hg surveillance program for the National Health Service of Brazil, directed by Dr Elisabeth Santos at the Evandro Chagas Institute (IED), the leading federal biomedical research institute in Amazonian Brazil. Her laboratory has characterized the sources and levels of exposures to Hg in thousands of persons residing in the Amazonian states of Amazonas, Rondonia, Amapa, Acre, and Para (e.g., Santos et al., 2000). Some of these populations have been exposed directly to elemental and iHg through amalgamation

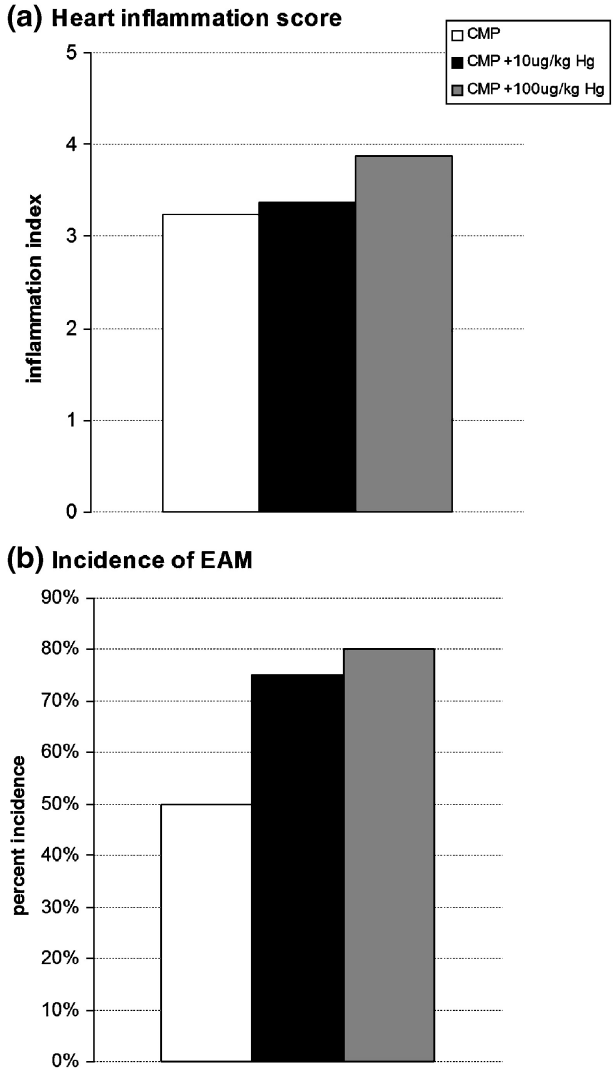

Fig. 3. Effects of Hg pretreatment (200 μg/kg q.o.d. for 15 days) on both severity (a) and incidence (b) of cardiomyopathy induced by cardiac myosin peptide (CMP). In the absence of CMP, Hg had no effects on heart histopathology.

extraction of gold from placer deposits in rivers and streams (see Fig. 4 for illustrations of work practices involving amalgamation with elemental Hg and burning of amalgams). Exposures to Hg in these operations can be very high, although among gold miners, urine Hg levels are highly variable owing to the episodic nature of gold mining (Silbergeld et al., 2002; de Jesus et al., 2001). In a study, we conducted at a gold camp in the mid Tapajos River watershed in the state of Para, blood and urine Hg levels were substantially elevated (Fig. 5). Among gold processors (persons who burn amalgam, usually in towns), exposures result in urinary Hg levels 34 and 70 μg/L (de Jesus et al., 2001).

Our study of autoimmune biomarkers was conducted at two sites in the mid-Amazon region of the state of Para (see Fig. 4 for map). The study was conducted under approval from the Committee on Ethical Research of the FNS, and the institutional review board of the IEC, as well as approval by the IRB at the University of Maryland Medical School. Serum samples were collected from workers at Rio Rato, a gold mining site in the lower Tapajos watershed, and from adult residents of Tabatinga, a riverine community on the mid-Amazon with no Hg inputs and levels of Hg in fish similar to those found in fish from uncontaminated watersheds of North America.

We analyzed the sera for biomarkers of autoimmune dysfunction, by indirect immunofluorescence microscopy using human epithelial cells (HEp-2) as substrate, following the methods of Burek and Rose (1995). As shown in Fig. 6, ANoA levels were significantly elevated in persons from Rio Rato, as compared to those from Tabatinga. In adults from Tabatinga, the prevalence of detectable ANA or ANoA was similar to those reported for North American and Brazilian populations without disease. Moreover, in 14 persons from Rio Rato, elevations were observed in both ANA and ANoA. Increased prevalence of elevated ANoA was related to length of time in gold mining (a better measure of exposure than spot urine, in our experience and that of our colleagues (de Jesus et al., 2001) and also to self-reported history of past malaria infection. No information is available from this study about possible autoimmune disease; however, a standard clinical examination in the field did not reveal overt pathophysiology or symptom complaints suggestive of any serious disease.

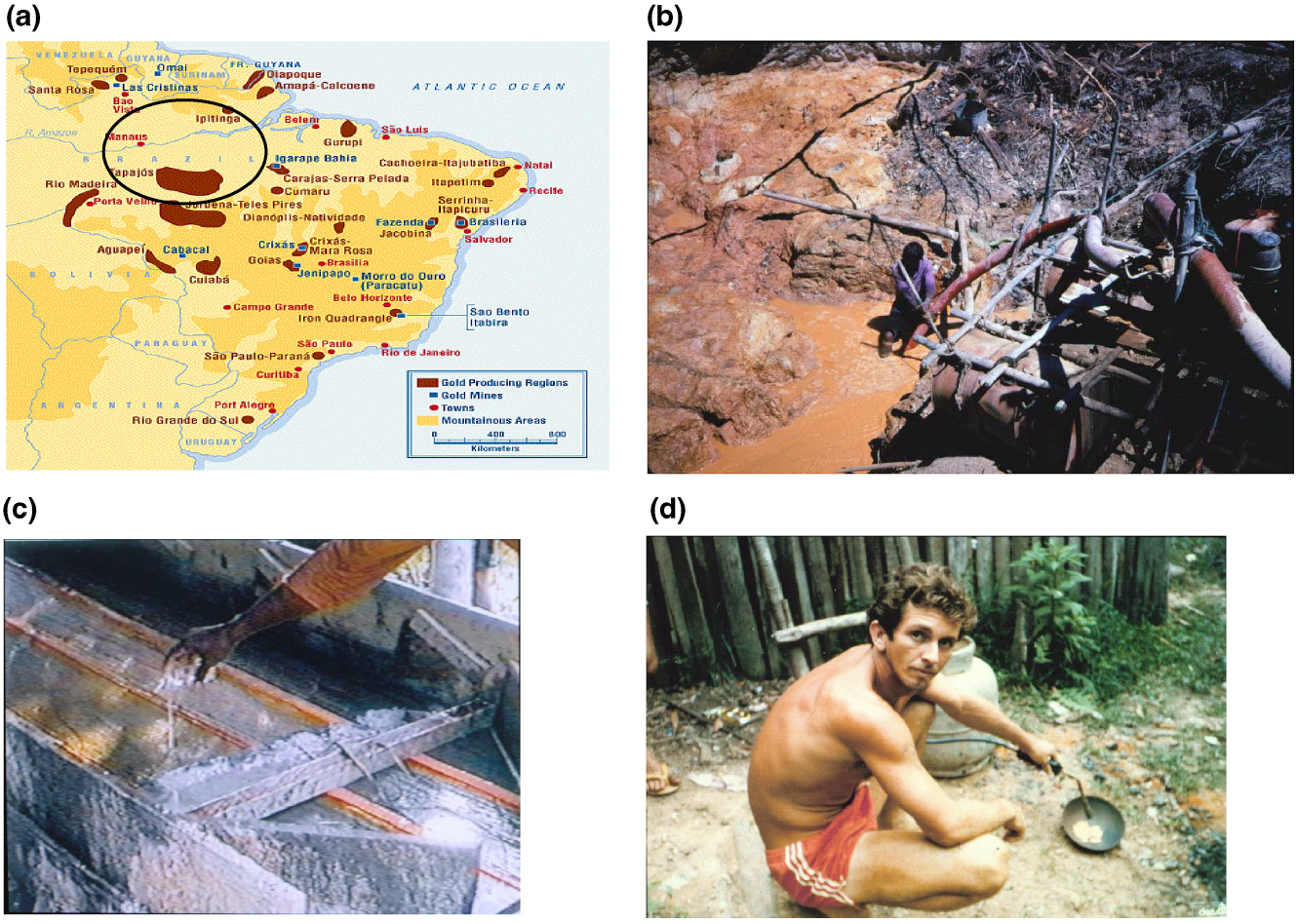

Fig. 4. Small scale gold mining operations in Amazonian Brazil. (a) Location of gold mining region in Para, Brazil; (b) hydraulic operations in a tributary of the Tapajos River; (c) addition of liquid mercury to washed sediments; (d) on site burning of amalgam at a gold camp. All photos taken by E. Silbergeld except for (c), courtesy of Dr David Cleary.

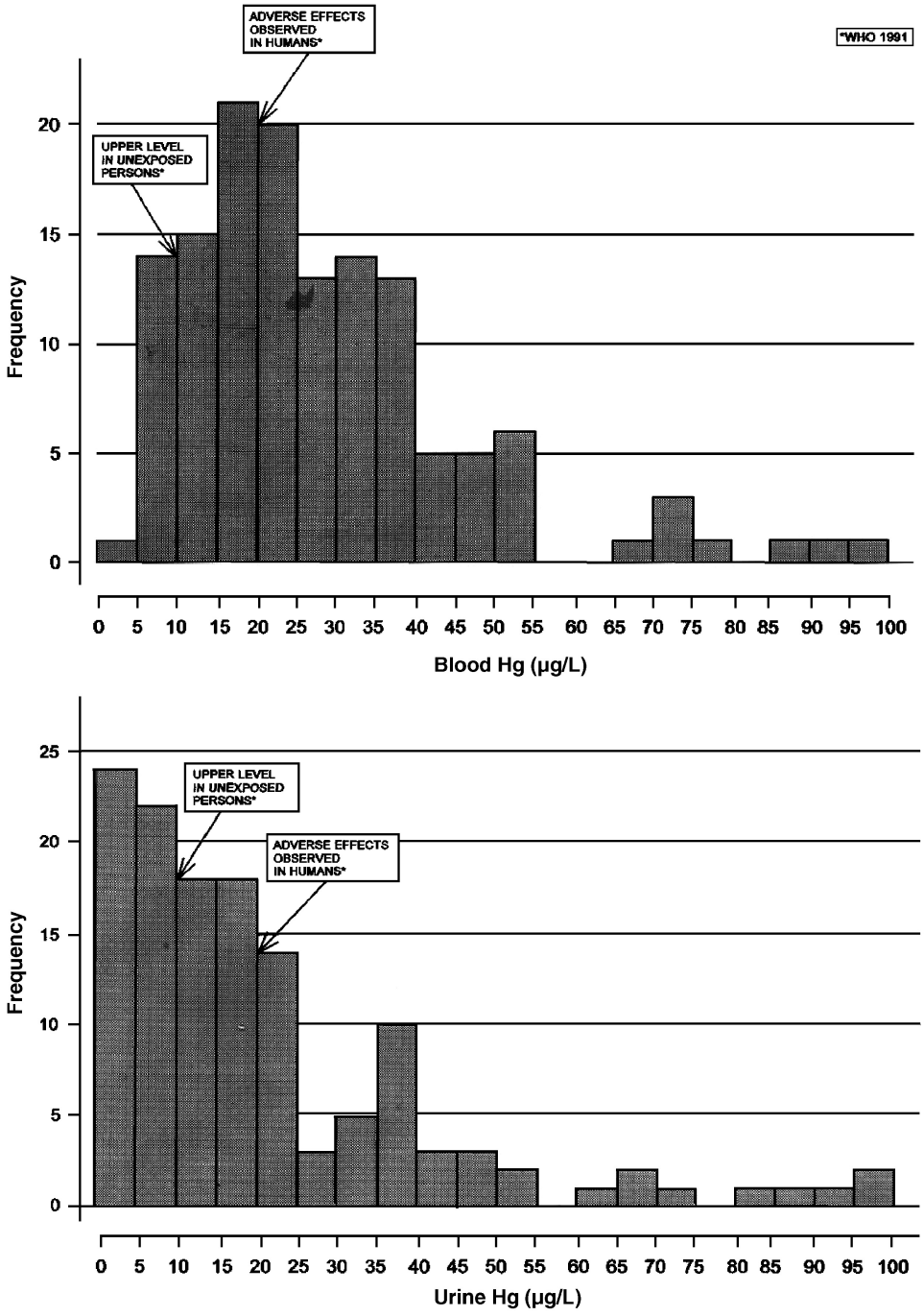

Fig. 5. Blood and urine mercury in gold miners studied at the "Piranha" camp, in 1999. Figure reprinted from Silva et al., 2004.

We have further analyzed these sera for antifibrillarin antibodies. In studies of mice exposed to Hg, it has been noted that antifibrillarin and other autoantibodies to small nucleolar ribonucleoprotein particles (snoRNPs) such as fibrillarin, may be sensitive and relatively specific (but not unique) biomarkers of Hg-induced immunotoxicity (Hultman et al., 1989; Hultman and Enestrom, 1992; Pollard et al., 1997; Monestier et al., 1994; Hultman and Hansson-Georgiadis, 1999; Takeuchi et al., 1995). Pollard's group has recently identified autoantibodies to other snoRNPs in addition to fibrillarin in mice exposed to Hg (Yang et al., 2001). In collaboration with Dr Pollard's lab, these sera are currently being analyzed for anti-fibrillarin autoantibodies. Preliminary data indicate that anti-fibrillarin autoantibodies were detected infrequently in miners with high Hg exposures and elevated ANA/ANoA. As shown in Fig. 6, these gels also demonstrate the presence of many additional, unidentified antibodies to nuclear proteins, as noted by Pollard's group in studies of mice. Identification of these other antibodies is ongoing.

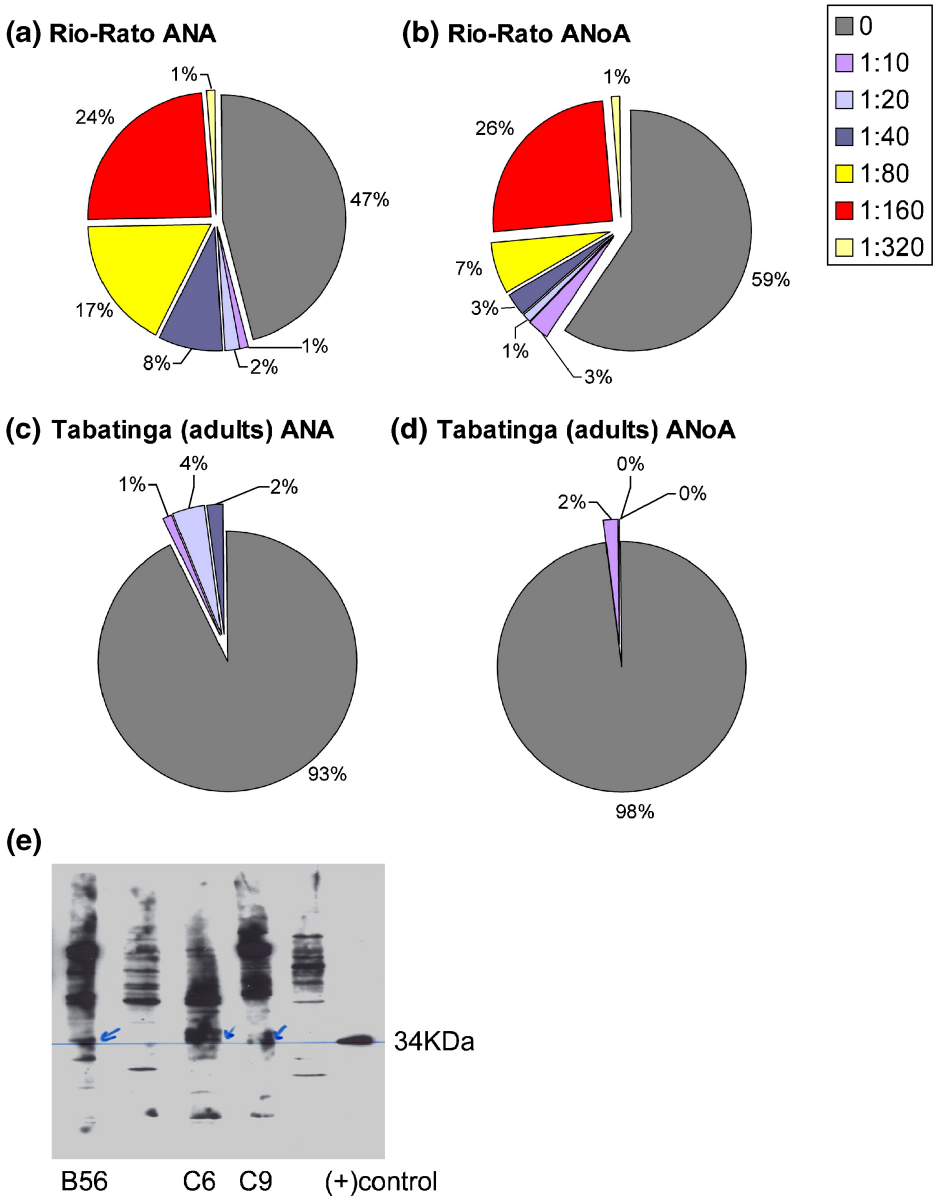

Fig. 6. Autoantibodies in serum from gold miners and a referent population in Amazonian Brazil (data from Silva et al., 2004). (a) and (b) ANA and ANoA in Rio Rato miners; (c) and (d) ANA and ANoA in Tabatinga referents; (e) antifibrillarin antibodies in Rio Rato miners with high Hg and high ANA/ANoA levels. Positive control sera were from scleroderma patients, courtesy of Dr K M Pollard. Figure reprinted from Silva et al., 2004.

These data support the association between Hg exposures and biomarkers of autoimmune dysfunction. These are the first data to suggest that Hg exposures in humans may induce similar dysfunctions as reported in rodent models of Hg immunotoxicity. While we were able to exclude the possible influence of undernutrition and substance abuse, based upon questionnaire information and dietary history, there may be specific reasons for this observation in this population. First, the gold miners and burners in Rio Rato were exposed to infectious diseases, in addition to Hg: over 95% had prevalent malaria at the time of our study, and 100% reported past malaria infections. Second, exposures to iHg were episodic and likely to involve very high intermittent doses associated with inhalation of elemental and iHg. Third, the possible contribution of immunogenetic determinants to susceptibility to Hg cannot be excluded. The populations sampled are highly diverse, with many individuals having European, African, and/or indigenous ancestry.

Implications of Hg-induced autoimmune dysfunction

These results are consistent with our hypothesis, also advanced by Fournie et al. (2001), that Hg by itself may not induce autoimmune disease or autoimmune dysfunction except under special circumstances, such as genetic predisposition as demonstrated in lupus-prone mice. Nothing is known of variations in human susceptibility to Hg

immunotoxicity. Our studies of autoimmune disease in mice expand the concept of "predisposition" to include exposures to triggering events, such as infection or antigen exposure. In mice, exposure of nonsusceptible mouse strains to Hg prior to the induction of an allogeneic GVHD greatly accelerates lupus-like disease. Similarly, exposure of mice to Hg prior to inoculation with the myocarditis producing antigen CMP increases the incidence and severity of experimental autoimmune myocarditis, an effect not seen with Hg treatment alone.

There are several implications of Hg-induced autoimmune dysfunction for public health, which support continued research in both animal models and human populations. First, in the animal models, the interactions of iHg with either intrinsic or acquired predisposition to autoimmune disease are some of the lowest effects yet described. Doses as low as 20 μg/kg for 2 weeks (Via et al., 2003) or about 2 μg/kg/day for several months (Pollard et al., 1999) are associated with significant exacerbation or acceleration of autoimmune disease, including severe pathophysiology and premature death. The no observable adverse effect level (NOAEL) for these outcomes has not been defined. Second, the immunotoxic effects of Hg show clear interactions with immunogenotype in mice and rats, which raises questions about genetic susceptibility to Hg in human populations. The possibility of genetic determinants of human susceptibility to Hg has not been investigated, but it is reasonable to suspect that such gene–environment interactions that affect both disease incidence and severity may occur among humans. Third, the immunotoxic effects of Hg compounds have been reported for iHg as well as several organic species of Hg, including ethylmercury, which is still utilized in some vaccine preparations (Havarinasab et al., 2004), which raises the possibility that many types of Hg exposures may be equivalently immunotoxic and that they may be cumulative in their impacts on the immune system. Fourth, the possibility that neuroimmunologic mechanisms may be involved in inhibition of neuronal migration may have implications for both early and later neurotoxicity; that is, by inhibiting contributions of new neurons from the stem cell pool, Hg may contribute to the risks of neurodegenerative disease (Weiss et al., 2002). The possibility that the mechanisms of other target organ toxicity associated with Hg may involve immunological signaling suggests that Hg-induced alterations in immune system function may have relevance to understanding the toxicity of Hg more generally.

References

Abedi-Valugerdi, M., Hu, H., Moller, G., 1997. Mercury-induced renal immune complex deposits in young (NZB × NZW)F1 mice: characterization of antibodies/autoantibodies. Clin. Exp. Immunol. 110, 86–91.

Al-Balaghi, S., Moller, E., Moller, G., Abedi-Valugerdi, M., 1996. Mercury induces polyclonal B cell activation, autoantibody production and renal immune complex deposits in young (NZB × NZW)F1 hybrids. Eur. J. Immunol. 26, 1519–1526.

Arnett, F.C., Fritzler, M.J., Ahn, C., Holian, A., 2000. Urinary mercury levels in patients with autoantibodies to U3-RNP (fibrillarin). J. Rheumatol. 27, 405–410.

Aucott, M., McLinden, M., Winka, M., 2003. Release of mercury from broken fluorescent bulbs. J. Air Waste Manage. Assoc. 53, 143–151.

Aymaz, S., Gross, O., Krakamp, B., Ortmann, M., Dienes, H.P., Weber, M., 2001. Membranous nephropathy from exposure to mercury in the fluorescent-tube-recycling industry. Nephrol. Dial. Transplant 16, 2253–2255.

Barregard, L., Enestrom, S., Ljunghusen, O., Wieslander, J., Hultman, P., 1997. A study of autoantibodies and circulating immune complexes in mercury-exposed chloralkali workers. Int. Arch. Occup. Environ. Health 70, 101–106.

Barregard, L., Svalander, C., Schutz, A., Westberg, G., Sallsten, G., Blohme, I., Molne, J., Attman, P.O., Haglind, P., 1999. Cadmium, mercury, and lead in kidney cortex of the general Swedish population: a study of biopsies from living kidney donors. Environ. Health Perspect. 107, 867–871.

Beuter, A., Edwards, R., 2004. Effect of chronic exposure to methylmercury on eye movements in Cree subjects. Int. Arch. Occup. Environ. Health 77, 97–107.

Bigazzi, P.E., 1994. Autoimmunity and heavy metals. Lupus 3, 449–453.

Burbacher, T.M., Rodier, P.M., Weiss, B., 1990. Methylmercury developmental neurotoxicity: a comparison of effects in humans and animals. Neurotoxicol. Teratol. 12, 191–202.

Burek, C.L., Rose, N.R., 1995. Autoantibodies. In: Colvin, R., Bhan, A., McCluskey, R. (Eds.), Diagnostic Immunopathology. Raven Press, New York, pp. 207–230.

Calderon-Aranda, E.S., Jedlicka, A., Scott, A., Silbergeld, E.K., 2004. Gene expression analysis of the mice cerebellar cells exposed to methlymercury. Toxicol. Sci. 78, 233.

Clarkson, T.W., 1997. The toxicology of mercury. Crit. Rev. Clin. Lab. Sci. 34, 369–403.

Clarkson, T.W., Magos, L., Myers, G.J., 2003. The toxicology of mercury-current exposures and clinical manifestations. N. Engl. J. Med. 349, 1731–1737.

Cohen, M., Artz, R., Draxler, R., Miller, P., Poissant, L., Niemi, D., Ratte, D., Deslauriers, M., Duval, R., Laurin, R., Slotnick, J., Nettesheim, T., McDonald, J., 2004. Modeling the atmospheric transport and deposition of mercury to the Great Lakes. Environ. Res. 95, 247–265.

Cooper, G.S., Miller, F.W., Pandey, J.P., 1999. The role of genetic factors in autoimmune disease: implications for environmental research. Environ. Health Perspect. 107 (Suppl. 5), 693–700.

Damstra, T., 2002. Potential effects of certain persistent organic pollutants and endocrine disrupting chemicals on the health of children. J. Toxicol., Clin. Toxicol. 40, 457–465.

Dantas, D.C., Queiroz, M.L., 1997. Immunoglobulin E and autoantibodies in mercury-exposed workers. Immunopharmacol. Immunotoxicol. 19, 383–392.

de Jesus, I.M., de Oliveira Santos, E.C., da Silva Brabo, E., Loureiro, E.C., de Magalhaes Camara, V., Mascarenhas, A.F., da Silva, D.F., Cleary, D., 2001. Exposure to elemental mercury in urban workers and gold miners from the Tapajos Region, Para, Brazil. Bull. Environ. Contam. Toxicol. 67, 317–323.

Druet, P., 1989. Contribution of immunological reactions to nephrotoxicity. Toxicol. Lett. 46, 55–64.

Ely, J.T., 2001. Mercury induced Alzheimer's disease: accelerating incidence? Bull. Environ. Contam. Toxicol. 67, 800–806.

EPA, 1997. Mercury Study Report to Congress. Volume II: An Inventory of Anthropogenic Mercury Emissions in the United StatesUS Environmental Protection Agency, Washington.

Fairweather, D., Kaya, Z., Shellam, G.R., Lawson, C.M., Rose, N.R., 2001. From infection to autoimmunity. J. Autoimmun. 16, 175–186.

Faustman, E.M., Ponce, R.A., Ou, Y.C., Mendoza, M.A., Lewandowski, T., Kavanagh, T., 2002. Investigations of methylmercury-induced

alterations in neurogenesis. Environ. Health Perspect. 110 (Suppl. 5), 859–864.
Fournie, G.J., Mas, M., Cautain, B., Savignac, M., Subra, J.F., Pelletier, L., Saoudi, A., Lagrange, D., Calise, M., Druet, P., 2001. Induction of autoimmunity through bystander effects. Lessons from immunological disorders induced by heavy metals. J. Autoimmun. 16, 319–326.
Gochfeld, M., 2003. Cases of mercury exposure, bioavailability, and absorption. Ecotoxicol. Environ. Saf. 56, 174–179.
Grandjean, P., Weihe, P., White, R.F., Debes, F., Araki, S., Yokoyama, K., Murata, K., Sorensen, N., Dahl, R., Jorgensen, P.J., 1997. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. Neurotoxicol. Teratol. 19, 417–428.
Griem, P., Gleichmann, E., 1995. Metal ion induced autoimmunity. Curr. Opin. Immunol. 7, 831–838.
Hatten, M.E., 2002. New directions in neuronal migration. Science 297, 1660–1663.
Havarinasab, S., Lambertsson, L., Qvarnstrom, J., Hultman, P., 2004. Dose-response study of thimerosal-induced murine systemic autoimmunity. Toxicol. Appl. Pharmacol. 194, 169–179.
Hornig, M., Chian, D., Lipkin, W.I., 2004. Neurotoxic effects of postnatal thimerosal are mouse strain dependent. Mol. Psychiatry 9, 833–845.
Hultman, P., Enestrom, S., 1992. Dose-response studies in murine mercury-induced autoimmunity and immune-complex disease. Toxicol. Appl. Pharmacol. 113, 199–208.
Hultman, P., Hansson-Georgiadis, H., 1999. Methyl mercury-induced autoimmunity in mice. Toxicol. Appl. Pharmacol. 154, 203–211.
Hultman, P., Nielsen, J.B., 2001. The effect of dose, gender, and non-H-2 genes in murine mercury-induced autoimmunity. J. Autoimmun. 17, 27–37.
Hultman, P., Pollard, K.M., 1996. Fibrillarin autoantibodies. In: Peters, J., Shoenfeld, Y. (Eds.), Autoantibodies. Elsevier, Amsterdam, pp. 253–265.
Hultman, P., Enestrom, S., Pollard, K.M., Tan, E.M., 1989. Anti-fibrillarin autoantibodies in mercury-treated mice. Clin. Exp. Immunol. 78, 470–477.
Iregren, A., Andersson, M., Nylen, P., 2002. Color vision and occupational chemical exposures: I. An overview of tests and effects. Neurotoxicology 23, 719–733.
Lacerda, L.D., de Souza, M., Ribeiro, M.G., 2004. The effects of land use change on mercury distribution in soils of Alta Floresta, Southern Amazon. Environ. Pollut. 129, 247–255.
Langworth, S., Elinder, C.G., Sundquist, K.G., Vesterberg, O., 1992. Renal and immunological effects of occupational exposure to inorganic mercury. Br. J. Ind. Med. 49, 394–401.
Lauwerys, R., Bernard, A., Roels, H., Buchet, J.P., Gennart, J.P., Mahieu, P., Foidart, J.M., 1983. Anti-laminin antibodies in workers exposed to mercury vapour. Toxicol. Lett. 17, 113–116.
Lawrence, D.A., McCabe Jr., M.J., 2002. Immunomodulation by metals. Int. Immunopharmacol. 2, 293–302.
Lie, D.C., Song, H., Colamarino, S.A., Ming, G.L., Gage, F.H., 2004. Neurogenesis in the adult brain: new strategies for central nervous system diseases. Annu. Rev. Pharmacol. Toxicol. 44, 399–421.
Lodenius, M., Malm, O., 1998. Mercury in the Amazon. Rev. Environ. Contam. Toxicol. 157, 25–52.
Mahaffey, K.R., 2000. Recent advances in recognition of low-level methylmercury poisoning. Curr. Opin. Neurol. 13, 699–707.
Mahaffey, K.R., Clickner, R.P., Bodurow, C.C., 2004. Blood organic mercury and dietary mercury intake: national health and nutrition examination survey, 1999 and 2000. Environ. Health Perspect. 112, 562–570.
Marin, O., Rubenstein, J.L., 2003. Cell migration in the forebrain. Annu. Rev. Neurosci. 26, 441–483.
Meij, R., Vredenbregt, L.H., te Winkel, H., 2002. The fate and behavior of mercury in coal-fired power plants. J. Air Waste Manage. Assoc. 52, 912–917.
Monestier, M., Losman, M.J., Novick, K.E., Aris, J.P., 1994. Molecular analysis of mercury-induced antinucleolar antibodies in H-2S mice. J. Immunol. 152, 667–675.
Moszczynski, P., 1999. Immunological disorders in men exposed to metallic mercury vapour. A review. Cent. Eur. J. Public Health 7, 10–14.
Moszczynski, P., Rutowski, J., Slowinski, S., Bem, S., Jakus-Stoga, D., 1996. Effects of occupational exposure to mercury vapors on T-cell and NK-cell populations. Arch. Med. Res. 27, 503–507.
Myers, G.J., Davidson, P.W., Shamlaye, C.F., Axtell, C.D., Cernichiari, E., Choisy, O., Choi, A., Cox, C., Clarkson, T.W., 1997. Effects of prenatal methylmercury exposure from a high fish diet on developmental milestones in the Seychelles Child Development Study. Neurotoxicology 18, 819–829.
NRC, 2000. Toxicological Effects of Methyl Mercury. NAS Press, Washington.
Nyland, J.F., Fairweather, D., Rose, N.R., Silbergeld, E.K., 2004. Inorganic mercury increases severity and frequency of autoimmune myocarditis in mice. Toxicol. Sci. 78, 12.
Pietsch, P., Vohr, H.W., Degitz, K., Gleichmann, E., 1989. Immunological alterations inducible by mercury compounds: II. $HgCl_2$ and gold sodium thiomalate enhance serum IgE and IgG concentrations in susceptible mouse strains. Int. Arch. Allergy Appl. Immunol. 90, 47–53.
Pollard, K.M., Lee, D.K., Casiano, C.A., Bluthner, M., Johnston, M.M., Tan, E.M., 1997. The autoimmunity-inducing xenobiotic mercury interacts with the autoantigen fibrillarin and modifies its molecular and antigenic properties. J. Immunol. 158, 3521–3528.
Pollard, K.M., Pearson, D.L., Hultman, P., Hildebrandt, B., Kono, D.H., 1999. Lupus-prone mice as models to study xenobiotic-induced acceleration of systemic autoimmunity. Environ. Health Perspect. 107 (Suppl. 5), 729–735.
Pollard, K.M., Pearson, D.L., Hultman, P., Deane, T.N., Lindh, U., Kono, D.H., 2001. Xenobiotic acceleration of idiopathic systemic autoimmunity in lupus-prone bxsb mice. Environ. Health Perspect. 109, 27–33.
Potter, W.E., 2002. Does elemental mercury exist in the workplace? Health Phys. 83, S30–S31.
Powell, J.J., Van de Water, J., Gershwin, M.E., 1999. Evidence for the role of environmental agents in the initiation or progression of autoimmune conditions. Environ. Health Perspect. 107 (Suppl. 5), 667–672.
Rice, D., Barone Jr., S., 2000. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environ. Health Perspect. 108 (Suppl. 3), 511–533.
Robinson, C.J., White, H.J., Rose, N.R., 1997. Murine strain differences in response to mercuric chloride: antinucleolar antibodies production does not correlate with renal immune complex deposition. Clin. Immunol. Immunopathol. 83, 127–138.
Rose, N.R., 2002. Mechanisms of autoimmunity. Semin. Liver Dis. 22, 387–394.
Santos, E.C., Jesus, I.M., Brabo, E.S., Loureiro, E.C., Mascarenhas, A.F., Weirich, J., Camara, V.M., Cleary, D., 2000. Mercury exposures in riverside Amazon communities in Para, Brazil. Environ. Res. 84, 100–107.
Sass, J.B., Haselow, D.T., Silbergeld, E.K., 2001. Methylmercury-induced decrement in neuronal migration may involve cytokine-dependent mechanisms: a novel method to assess neuronal movement in vitro. Toxicol. Sci. 63, 74–81.
Schober, S.E., Sinks, T.H., Jones, R.L., Bolger, P.M., McDowell, M., Osterloh, J., Garrett, E.S., Canady, R.A., Dillon, C.F., Sun, Y., Joseph, C.B., Mahaffey, K.R., 2003. Blood mercury levels in US children and women of childbearing age, 1999–2000. JAMA 289, 1667–1674.
Silbergeld, E.K., Nash, D., Trevant, C., Strickland, G.T., de Souza, J.M., da Silva, R.S., 2002. Mercury exposure and malaria prevalence among gold miners in Para, Brazil. Rev. Soc. Bras. Med. Trop. 35, 421–429.
Silva, I.A., Nyland, J.F., Gorman, A., Perisse, A., Ventura, A.M., Santos, E.C., de Souza, J.M., Burek, C.L., Rose, N.R., Silbergeld, E.K., 2004.

Mercury exposure, malaria, and serum antinuclear/antinucleolar antibodies in amazon populations in Brazil: a cross-sectional study. Environ. Health 3, 11–22.

Soleo, L., Vacca, A., Vimercati, L., Bruno, S., Di Loreto, M., Zocchetti, C., Di Stefano, R., Candilio, G., Lasorsa, G., Franco, G., Foa, V., 1997. Minimal immunological effects on workers with prolonged low exposure to inorganic mercury. Occup. Environ. Med. 54, 437–442.

Sweet, L.I., Zelikoff, J.T., 2001. Toxicology and immunotoxicology of mercury: a comparative review in fish and humans. J. Toxicol. Environ. Health, B Crit. Rev. 4, 161–205.

Takeuchi, K., Turley, S.J., Tan, E.M., Pollard, K.M., 1995. Analysis of the autoantibody response to fibrillarin in human disease and murine models of autoimmunity. J. Immunol. 154, 961–971.

van Veizen, D., Langenkamp, H., Herb, G., 2002. Review: mercury in waste incineration. Waste Manage. Res. 20, 556–568.

Via, C.S., Nguyen, P., Niculescu, F., Papadimitriou, J., Hoover, D., Silbergeld, E.K., 2003. Low-dose exposure to inorganic mercury accelerates disease and mortality in acquired murine lupus. Environ. Health Perspect. 111, 1273–1277.

Vimercati, L., Santarelli, L., Pesola, G., Drago, I., Lasorsa, G., Valentino, M., Vacca, A., Soleo, L., 2001. Monocyte-macrophage system and polymorphonuclear leukocytes in workers exposed to low levels of metallic mercury. Sci. Total Environ. 270, 157–163.

Warfvinge, K., Hansson, H., Hultman, P., 1995. Systemic autoimmunity due to mercury vapor exposure in genetically susceptible mice: dose–response studies. Toxicol. Appl. Pharmacol. 132, 299–309.

Weiss, B., Clarkson, T.W., Simon, W., 2002. Silent latency periods in methylmercury poisoning and in neurodegenerative disease. Environ. Health Perspect. 110 (Suppl. 5), 851–854.

WHO, 1991. Methyl Mercury. IPCS, Geneva.

Yang, J.M., Baserga, S.J., Turley, S.J., Pollard, K.M., 2001. Fibrillarin and other snoRNP proteins are targets of autoantibodies in xenobiotic-induced autoimmunity. Clin. Immunol. 101, 38–50.

Yokoo, E.M., Valente, J.G., Grattan, L., Schmidt, S.L., Platt, I., Silbergeld, E.K., 2003. Low level methylmercury exposure affects neuropsychological function in adults. Environ. Health 2, 8.

Zeitz, P., Orr, M.F., Kaye, W.E., 2002. Public health consequences of mercury spills: Hazardous Substances Emergency Events Surveillance system, 1993–1998. Environ. Health Perspect. 110, 129–132.