CAN MERCURY CAUSE IMMUNE SYSTEM DYSFUNCTION?

Compiled by Robert Gammal (Feb 2013)

Almost all government health agencies around the world advise that amalgam should not be placed in people with a compromised immune system. The World Health Organization makes the same recommendation. In Australia the National Health and Medical Research Council make the same recommendation. Even the Manufacturers recommend against using their products in people with a compromised immune system. The only people, who still think it is a good idea to poison immune-compromised patients, are the teachers of dentistry in many universities. This is a madness that the deans and professors cannot ignore. The plea of ignorance is of little comfort to those people whose health is being compromised even further by the supposed state of the art filling material. Mercury is a poison. It makes people sick. It is really very simple.

Dorland's Medical Dictionary defines "hypersensitivity" as: "A state of altered reactivity in which the body reacts with an exaggerated immune response to a foreign agent." Poisons, or toxins, on the other hand can effect all body structures, not just the immune system. Although mercury does have a profound adverse effect on the immune system, it is considered to be a poison, not solely an allergen. The attempts of the dental profession to limit consideration of amalgam mercury exposure to immune system effects constitutes nothing more than a diversion to hide behind a facade. (BIO-PROBE NEWS LETTER 2 MAY 1997)

The immune system of many animals, including man, is affected by mercury in any of its forms.

There is direct evidence that mercury can cause lymphocyte chromosomal abnormalities. There is definite evidence that the ratios of the different types of lymphocytes change with deleterious consequences. Autoimmune type reactions have been shown in animal models. Antinuclear antibodies have been induced by mercury as well as polygonal B cells. This autoimmune process results in monoclonal antibodies being produced. Prolonged action of low mercury concentrations leads to changes in a number of immunological indicators: Agglutinin titters, active leukocytes percent, phagocytic number, complement activity, and the items described above. Thus mercury compounds are immunomodulatory and the decrease in B-cell function indicates toxicity.

A small taste of some of the published science follows (current to February 2013).

1. HUTCHINSON F., RAFFLE E. J. AND MACLEOD T. M. (1972) THE SPECIFICITY OF IYMPHOCYTE TRANSFORMATION IN VITRO BY NICKEL SALTS IN NICKEL SENSITIVE SUBJECTS. JOURNAL OF INVESTIGATIVE DERMATOLOGY 58, 362-365.

2. KELCHNER J MCINTOSH JR BOEDECKER E GUGGENHEIM S MCINTOSH RM EXPERIMENTAL AUTOLOGOUS IMMUNE DEPOSIT NEPHRITIS IN RATS ASSOCIATED WITH MERCURIC CHLORIDE ADMINISTRATION. EXPERIENTIA (1976 SEP 15) 32(9):1204-8

   Serial administration of mercuric chloride to rats was followed by development of antibodies to tubular basement membrane and renal tubular epithelial antigen (RTE) and glomerulonephritis characterized by granular deposits of hosts IgG, C3 and RTE

along the glomerular capillary walls. The glomerular fixed antibody was directed against RTE. These studies suggest that tubular injury by mercury may lead to release of RTE and autosensitization and subsequent antibody production to this antigen result in formation of and glomerular deposition of circulating immunopathogenic complexes (RTE-anti-RTE) and glomerular morphologic alterations.

3. Barabas AZ Alexander F Lannigan R Induction of an autologous immune-complex glomerulonephritis in the rat by intravenous injection of heterologous anti-rat kidney tubular antibody IV: Effect of injection of HgCl2 prior to the antibody. Br J Exp Pathol (1976 Oct) 57(5):555-9

   Autologous immune-complex glomerulonephritis developed in rats injected s.c. with HgCl2 2 days before the injection of anti-tubular fraction 3 antibody. The glomerulonephritis was progressive and characterized by granular deposition of IgG and C-3, with proteinuria from the eighth week onwards. Granular densities and severe glomerular basement membrane changes were observed when the experiment was terminated after 9 months. A possible mechanism of the glomerular lesion is discussed.

4. Druet P Druet E Potdevin F Sapin C Immune type glomerulonephritis induced by HgCl2 in the Brown Norway rat. Ann Immunol (Paris) (1978 Oct-Dec) 129 C(6):777-92

   HgCl2 chronically injected in the Brown-Norway rat induced a biphasic renal disease. The first stage was characterized by anti-glomerular basement membrane antibodies. The second stage by the appearance of immune complexe type deposits in the glomerular tufts and in the small renal arteries. These immune complexes were constituted of a basement membrane component and anti-basement membrane antibodies. Other immune complexes were perhaps involved. In most of the rats, a proteinuria and a nephrotic syndrome appeared, as a consequence of this immune disease. No abnormalities were observed in Lewis rats, suggesting a role for a genetic control of this immune response.

5. The role of hypersensitivity and the immune response in influencing susceptibility to metal toxicity. Kazantzis G Environ Health Perspect (1978 Aug) 25:111-8

   The immune status of the individual is an additional variable which has to be taken into account in any consideration of factors which influence the metabolism and toxicity of metals. The commonly occurring phenomena are described resulting from increased cellular reactivity to platinum, mercury, gold, nickel, chromium, and beryllium, and an attempt has attempt has been made to classify these into the four types of immune response. The clinical effects can be very varied, giving rise to conjunctivitis, rhinitis, asthma, urticaria, contact dermatitis, proteinuria, nephrotic syndrome or blood dyscrasia. Of these effects, cutaneous hypersensitivity is the most common, affecting both industrial and general population groups. Metal compounds used in therapeutics and metals used in prostheses have also been responsible for hypersensitive reactions.

6. KOLLER LD EFFECTS OF ENVIRONMENTAL CONTAMINANTS ON THE IMMUNE SYSTEM. ADV VET SCI COMP MED (1979) 23:267-95

7. EXTRARENAL IMMUNE COMPLEX TYPE DEPOSITS INDUCED BY MERCURIC CHLORIDE IN THE BROWN NORWAY RAT. BERNAUDIN JF DRUET E BELAIR MF PINCHON MC SAPIN C DRUET P CLIN EXP IMMUNOL (1979 NOV) 38(2):265-73

It has been reported previously that HgCl2 chronically injected in the BN rat induced a biphasic renal disease. During the first stage, anti-glomerular basement membrane antibodies appeared and during the second stage, an immune-complex type glomerulonephritis was observed. In the present study, a systemic immune disease is described. During the first stage, antibasement membrane antibodies were observed in various extrarenal structures. Their localization has been found to depend mainly on the characteristics of the endothelium. During the second stage, immune-complex type deposits containing IgG and C3 were found in most vascular structures. Their localization did not apparently depend on the endothelial characteristics. Among the organs tested the lung was most often spared. The occurrence of immune complex deposits was found to depend on the dose of HgCl2 injected: deposits were absent in some high dose HgCl2-injected rats but they were very numerous in low dose HgCl2-injected rats. These deposits probably have a pathogenic role although no major histological lesion could be found. This model may help to explain immune complex type deposits in systemic diseases.

8. TERATOGENIC AND GENETIC EFFECTS OF MERCURY TOXICITY. THE BIOCHEMISTRY OF MERCURY IN THE ENVIRONMENT. KHERA ET AL., NRIAGU, J.O.ED AMSTERDAM ELSEVIER, 503-18,1979

9. ACUTE METHYL MERCURY INTOXICATION IN MICE-- EFFECT ON THE IMMUNE SYSTEM. HIROKAWA K HAYASHI Y ACTA PATHOL JPN (1980 JAN) 30(1):23-32

10. IMMUNOREGULATION AND ANTI-NUCLEAR ANTIBODIES IN MERCURY-INDUCED GLOMERULOPATHY IN THE RAT. WEENING JJ HOEDEMAEKER PJ BAKKER WW CLIN EXP IMMUNOL (1981 JUL) 45(1):64-71

The pathogenesis of drug-induced autoimmune antibodies is in most cases uncertain. The recent demonstration of T cell aberrations in human and experimental drug-induced autoimmune disease suggests that immunodysregulation might form the basis of an uncontrolled B cell autoreactivity leading to autoantibody production. In the present study, lymphocytic stimulation by phytohemagglutinin (PHA) and concanavalin A-activated suppressor cell activity was measured in an experimental model of mercury-induced immune complex glomerulopathy associated with anti-nuclear antibodies and vasculitis in PVG/c rats. Both general T cell reactivity to PHA and concanavalin A-activated suppressor function as measured by a syngeneic target cell assay were found to be significantly decreased in mercury-diseased rats as compared with saline-injected control rats. Furthermore, the effect of neonatal and adult thymectomy on the course of the mercury-induced disease was studied. Anti-nuclear antibody activity and glomerular immune aggregate formation were found to be accelerated considerably by neonatal thymectomy, whereas thymectomy at adult age had no significant effect on the interval between the start of mercury administration and the appearance of serological and renal abnormalities. From the results it is concluded that mercury affects

both effector and regulatory T cell functions and that immunodysregulation seems to be of pathogenetic significance in this model of drug-induced disease.

11. Capron M Ayed K Druet E Sapin C Mandet C Druet P Girard JF Complement studies in BN rats with mercuric chloride-induced immune glomerulonephritis. Ann Immunol (Paris) (1980 Jul-Aug) 131D(1):43-55

    Whole complement haemolytic activity (CH50) changes were examined in 71 rats, developing and HgCl2-induced biphasic immune glomerulonephritis. In some rats, serum C4 level was also studied. Whole CH50 level was compared with proteinuria and C3 glomerular deposits. In control rats or in rats injected with low doses of HgCl2, there was no complement decrease. In rats injected with a high dose, after an initial increase (also observed in controls), CH50 level decreased between day 12 and day 20, sometimes dramatically. This decrease, observed during the first phase, was transient, CH50 levels returning to normal before day 30. Serum C4 level varied in accordance with CH50, indicating a classical pathway activation of complement. Fall in CH 50 and proteinuria was correlated: the heavier the proteinuria, the greater the fall in complement ($p < 0.01$). Whether proteinuria is or is not the consequence of the complement activation, remains to be demonstrated.

12. Mercury induced immune complex glomerulopathy: an experimental study. Weening JJ, et al. Chapter 4: pp 36-66. VanDendergen, 1980.

13. Inhalation or ingestion of organic or inorganic mercurials produces auto-immune disease in rats. Bernaudin JF Druet E Druet P Masse R Clin Immunol Immunopathol (1981 Jul) 20(1):129-35

14. Oral lichen planus and contact allergy to mercury. Finne K., Goransson K. and Winckler L. (1982) International Journal of Oral Surgery 11, 236- 239.

15. Polyclonal effect of HgCl2 in the rat, its possible role in an experimental autoimmune disease. Hirsch F Couderc J Sapin C Fournie G Druet P Eur J Immunol (1982 Jul) 12(7):620-5

    Mercuric chloride induces an autoimmune glomerulonephritis in Brown- Norway (BN) but not in Lewis (LEW) rats. Injection of HGCl2 into BN rats regularly produced a transient appearance of plaque-forming cells (PFC) of anti-2,4,6-trinitrophenyl and anti-sheep red blood cell specificity and circulating anti-single-stranded DNA antibodies. Addition of HgCl2 to spleen cell cultures from BN rats induced an increase in anti-trinitrophenyl PFC and reverse PFC. This effect was no longer observed when nylon wool column-depleted or anti-Thy-1 antiserum-treated spleen cells were cultured in the presence of HgCl1. These data suggest that HgCl2 acts as a polyclonal activator on spleen cells in BN rats, but not on isolated B lymphocytes. In contrast, no effect of HgCl2 on immunoglobulin production was observed in LEW rats. Since polyclonal activation and immune-type nephritis are both seen in BN but not in LEW rats, polyclonal activation may participate in the pathogenesis of the HgCl2-induced autoimmune disease of BN rats.

16. Immune complex type disease induced by HgCl2 in Brown-Norway rats: genetic control of susceptibility. Sapin: Clin Exp Immunol (1982 Jun) 48(3):700-4

17. Mercuric chloride induced autoimmune disease in Brown-Norway rats: sequential search for anti-basement membrane antibodies and circulating immune complexes. Bellon B Capron M Druet E Verroust P Vial MC Sapin C Girard JF Foidart JM Mahieu P Druet P Eur J Clin Invest (1982 Apr) 12(2):127-33

    Mercuric chloride induces in the Brown-Norway rat a biphasic autoimmune disease characterized initially by linear IgG deposits along the glomerular basement membrane followed later by granular IgG deposition. In the present study, anti-glomerular basement membrane antibodies and immune complex-like material were sequentially assessed in serial serum samples. Both were transiently found at the same period. Glomerular linear IgG deposits were present on day 11 but circulating anti-glomerular basement membrane antibodies were only found later on day 16. Circulating immune complexes were first detectable on day 8 before the earliest granular IgG deposits were first observed in the spleen vessels on day 16. The disappearance of circulating anti-glomerular basement membrane antibodies and of circulating immune complexes, although HgCl2 injections were pursued, is in agreement with the self-limited character of mercuric chloride induced autoimmune disease and suggests the induction of immunosuppressive mechanisms.

18. Effect of mercuric chloride on the proliferative response of human lymphocytes to cultured HeLa cells or a lectin. Ochi T Ohsawa M J Toxicol Sci (1982 Nov) 7(4):235-43

    Proliferative responses of human lymphocytes to cultured allogeneic HeLa cells and to PHA were employed as in vitro cellular immune systems to investigate effects of mercuric chloride on the both proliferative responses. When stimulator HeLa cells were pretreated with mercury, proliferative response of lymphocytes to HeLa cells in the mixed cell culture was suppressed dose-dependently. The response of lymphocytes treated with mercury to HeLa cells was suppressed markedly, even at 15-min exposure to 1 X 10(-5) M HgCl2. The response of lymphocytes to PHA as well as that to HeLa cells was suppressed by mercury treatment, even at 15-min exposure. A possible mechanism for the suppressive effect of mercury on the mixed cell reaction was discussed; mercury modification of molecules at the cell surface of the stimulator cells or responder cells and effects of mercury on macrophages.

19. Houssin D Druet E Hinglais N Verroust P Grossetete J Bariety J Druet P Glomerular and vascular IgG deposits in HgCl2 nephritis: role of circulating antibodies and of immune complexes. Clin Immunol Immunopathol (1983 Nov) 29(2):167-80

    The respective roles of circulating anti-glomerular basement membrane antibodies and of circulating immune complexes in the appearance of glomerular linear and granular IgG deposition during HgCl2-induced glomerulonephritis in the Brown-Norway rat has been studied. Syngeneic kidney transplantations have been performed at various phases of the disease. Results show that circulating antibodies are responsible for linear IgG deposition which did not change to granular deposits during the course of the disease. Electron-dense subepithelial deposits occurred only when circulating

immune complexes were detected. These experiments strongly suggest that, in the mercury model, circulating immune complexes are responsible for granular IgG deposits observed in arteries and in the subepithelial space of glomeruli.

20. HINGLAIS N GROSSETETE J PAING M DRUET P BARIETY J IMMUNOELECTRON MICROSCOPIC STUDY OF PLASMA PROTEIN PATHWAYS THROUGH THE ABNORMAL INTESTINAL VASCULATURE OF HGCL2 INDUCED IMMUNE DISEASE IN BROWN NORWAY RATS. VIRCHOWS ARCH A PATHOL ANAT HISTOPATHOL (1983) 400(3):277-86

Localization of immune deposits (ID) and the pathway of circulating serum proteins through the intestinal vasculature have been studied in 40 Brown Norway (BN) rats poisoned by mercuric chloride, using anti-peroxidase IgG as tracer. ID were found in all vessels but were initially detected along the epithelial basement membrane of villi and in pericytic venules and veins. ID were found in all the layers of the vessel walls. In pericytic or myocytic vessels, no ID were detected outside the adventitial lamina densa. ID trapped non immune IgG. Abnormal pathways were only found in venular capillaries and in pericytic venules with large gaps between endothelial junctions. ID were particularly abundant in these vessels.

21. MERCURIC CHLORIDE NEPHRITIS DEPENDS ON HOST RATHER THAN KIDNEY STRAIN. DRUET E HOUSSIN D DRUET P CLIN IMMUNOL IMMUNOPATHOL (1983 OCT) 29(1):141-5

Brown-Norway (BN) rats are susceptible to the induction of an autoimmune glomerulonephritis (GN) by HgCl2 while Lewis (LEW) rats are resistant. When a kidney from a LEW rat (nonsusceptible) is transplanted into a binephrectomized (LEW X BN)F1 hybrid (susceptible) then HgCl2 injections into the recipient result in GN developing in the donor kidney. When a kidney from a BN or (LEW X BN)F1 hybrid (susceptible) is transplanted into a nonsusceptible rat, injections of HgCl2 into the recipient do not result in GN in the donor kidney. These observations show that kidneys from nonsusceptible rats function as usceptible targets and that induction of the disease depends more on the host immune system than on modification of kidney determinants by HgCl2.

22. ENESTROM S HULTMAN P IMMUNE-MEDIATED GLOMERULONEPHRITIS INDUCED BY MERCURIC CHLORIDE IN MICE. EXPERIENTIA (1984 NOV 15) 40(11):1234-40

The BALB/c mouse developed mesangial deposits of immune constituents and light microscopical changes characteristic of immune complex glomerulonephritis after 8 weeks' treatment with mercuric chloride given by s.c. injection. There were no signs of linear of granular immune deposits along the glomerular capillary basement membrane after 2 or 8 weeks. The antigen could not be identified. No antibodies to nuclear or renal structures were found. Using a histochemical method (silver amplification) mercury was detected by light and electron microscopy in tubular and glomerular structures. Mercury was present in secondary lysosomes of the mesangial cells after eight weeks of mercury poisoning.

23. Michaud A Sapin C Leca G Aiach M Druet P Involvement of hemostasis during an autoimmune glomerulonephritis induced by mercuric chloride in brown Norway rats. Thromb Res (1984 Jan 1) 33(1):77-88

Mercuric chloride (HgCl2) induces in Brown Norway (BN) rats an autoimmune disease characterized by a biphasic glomerulonephritis (GN). A transient nephrotic syndrome occurs during the third and fourth weeks after the first HgCl2 injection. Related to nephrotic syndrome, an hypercoagulable state develops with decreased factor XII and anti-thrombin III (AT III) levels and increased factor V activity and fibrinogen concentration. Moreover, during the same period, most of the rats were found thrombocytopenic. The presence of soluble fibrin monomer complexes and of fibrin degradation products (FDP) in the plasma of these rats associated with fibrin thrombi in glomerular capillary lumen proved the occurrence of disseminated intravascular coagulation (DIC). DIC was responsible for the death of several rats but most of these survived and clotting abnormalities were no longer found. Numerous factors can explain the occurrence of DIC in this model: anti glomerular basement membrane antibodies, circulating immune complexes, complement activation and/or glomerular endothelial cell detachment. The HgCl2 induced autoimmune disease appears as a good experimental model to study the relation between coagulation process and glomerulonephritis.

24. Effect of dental amalgam and nickel alloys on T-lymphocytes: preliminary report. Eggleston DW J Prosthet Dent 1984 May;51(5):617-623

Preliminary data suggest that dental amalgam and dental nickel alloys can adversely affect the quantity of T-lymphocytes. Human T-lymphocytes can recognize specific antigens, execute effector functions, and regulate the type and intensity of virtually all cellular and humoral immune responses. Normal immune function depends on a proper quantity, quality, and ratio of T-lymphocyte helper and suppressor subsets. Further research may determine the frequency and magnitude of T-lymphocyte reduction and alteration by dental materials.

25. A survey of metal induced mutagenicity in vitro and in vivo Hansen K et al J Amer Coll Toxicol ., 1984:3;381-430

26. IgA-IgG disease in the intestines of rats ingesting HgCl", P. Andres, Clin Immun Immunopath, 30:488-494, 1984;

27. The mediation of mutagenicity and clastogenicity of heavy metals by physiochemical factors. Babich et al ., Environ Res., 1985:37;253-286

28. Effects of vitamin E and selenium deficiencies on rat immune function. Eskew ML Scholz RW Reddy CC Todhunter DA Zarkower A Immunology (1985 Jan) 54(1):173-80

The effects of dietary restriction of vitamin E and selenium were studied in male Long-Evans hooded rats. Weanling animals were maintained for 5-6 weeks on torula yeast-based diets, with or without the addition of vitamin E (150 IU/kg) or selenium (0.5 mg/kg), to form the following dietary groups: +E, +Se; +E, -Se; -E, +Se; -E, - Se, and a fifth group pair-fed with the -E, -Se group. This latter group exhibited a decreased rate of

growth similar to the -E, -Se group. Lymphocyte blastogenesis in response to mitogens was decreased in animals fed the diets deficient in either vitamin E or selenium, and also in the pair-fed group. Very marked suppression of mitogen responses was seen in the doubly deficient group, as well as a greater loss of viability during culture. Spleen cell-mediated antibody-dependent lysis of chicken erythrocytes was increased in the doubly deficient group, although this difference could be abolished by the addition of catalase, but not indomethacin, to the culture medium. Dietary deficiency of vitamin E and selenium had no discernible effects on alveolar macrophage function, as measured by cell-mediated antibody- dependent cytolysis, killing of Staphylococcus aureus or regulation of T- lymphocyte blastogenesis.

29. EDITORIAL. METAL CHELATION THERAPY, OXYGEN RADICALS AND HUMAN DISEASE. LANCET (1985). LANCET 19 JANUARY, PP. 143-145.

30. IN -VIVO SELF REACTIVITY OF MONONUCLEAR CELLS TO T CELLS AND MACROPHAGES EXPOSED TO HG CL2" L.PELLETIER ET AL.," EUR. J IMMUN.,1985:460-465;

31. THE MEDIATION OF MUTAGENICITY AND CLASTOGENICITY OF HEAVY METALS BY PHYSIO CHEMICAL FACTORS. BABICH ET AL ., ENVIRON RES., 1985:37;253-286

32. "AUTOREACTIVE T CELLS IN MERCURY INDUCED AUTOIMMUNE DISEASE", PELLETIER ET AL, J IMMUNOL,1986 137(8):2548-54 & SCAND J OF IMMUNOLOGY, 1990,31: 65-74

33. BEHAVORIAL AND NEUROPATHOLOGICAL EFFECTS OF PRENATAL METHYL MERCURY EXPOSURE IN MICE.. NOUYEM., MURAO K., KAJIWARA Y ., NEUROBEAHV.TOXICOL TERATOL. ,1985:7;227-232

34. CANDIDA, SILVER (MERCURY) FILLINGS AND THE IMMUNE SYSTEM RUSSELL-MANNING (ED.) GREENSWARD PRESS 1986. AMALGAM DENTAIRES ET ALLERGIES VERON ET AL J BIOL BUCCALE., 1986 : 14; 83-100

35. EFFECT OF PROSTAGLANDIN E1 IN BROWN NORWAY RATS WITH MERCURY-INDUCED AUTOIMMUNE DISEASE. HINGLAIS N PELLETIER L VIAL MC SAPIN C BASCOU C BARIETY J KELLEY V DRUET P CLIN IMMUNOL IMMUNOPATHOL (1986 SEP) 40(3):401-9

The effect of prostaglandin E1 on mercury-induced autoimmune disease in brown Norway rats has been investigated. Daily doses of 6 to 24 micrograms prolonged survival and significantly decreased proteinuria, deposition of immune reactants in the glomeruli, circulating anti-glomerular membrane antibody production, total serum IgE, and circulating immune complex level. A dose of 3 micrograms was also effective but to a lesser degree. These results show the efficiency of prostaglandin E1 in yet another autoimmune disease, show that the beneficial effect of prostaglandin E1 in this model is related to its immunosuppressive effects, and suggest that modification of prostaglandin-mediated suppression induced by HgCl2 might play a role in the pathogenesis of this autoimmune disease.

36. SELENIUM DEFICIENCY IN THE ACQUIRED IMMUNODEFICIENCY SYNDROME. DWORKIN B.M., ROSENTHAL W.S., WORMSER G.P. AND WEISS L. J PARENTER ENTERAL NUTR. 10(4):405-407, 1986.

ABSTRACT:

Severe protein-calorie malnutrition is common in patients with AIDS (acquired immunodeficiency syndrome). These nutritional deficits are likely to further impair immune responses and other organ functions vital for recovery from serious infectious diseases. Since selenium deficiency is known to be associated with oral candidiasis and abnormal phagocytic function in animals and depressed helper T-cell numbers in man, we evaluated both selenium status and other nutritional parameters in 12 patients with AIDS compared to 27 healthy controls. Selenium was measured by a spectroflourometric method. The mean (+SD) plasma selenium level in AIDS was 0.043 + 0.01 ug/ml vs 0.095 + 0.016 ug/ml in controls ($p < 0.001$). Whole blood selenium and red blood cell selenium levels were also signlficantly reduced in AIDS ($p < .005$). The mean weight loss in AIDS patients was 35.5 + 21.2 pounds. Serum albumin was significantly ($p < O.01$) lower in AIDS patients compared to controls. A good correlation between serum albumin and plasma selenium was noted ($r = 0.77$; $p < 0.001$). We conclude that selenium deficiency is a common component of the malnutrition seen in AIDS patlents. Therefore, aggressive nutritional support, includlng attention to selenium status should be considered an integral part of the therapy of AIDS patients.

Bio-Probe comment:

See Bio-Probe comments on the previous article above. Although not published as yet, we are aware of ongoing research demonstrating lower than normal levels of selenium and glutathione peroxidase in persons with amalgam fillings. Moreover, 5 months of therapeutic supplementation with selenium and glutathione were required to restore selenium and glutathione peroxidase values to their norms. After obtaining normal levels, the placement of one amalgam filling had an immediate effect of reducing selenium and glutathione peroxidase levels to their pre- supplementation values.

There presently exists a vast body of scientific data demonstrating the ability of mercury to affect the biochemical availability of both selenium and glutathione and their derivative enzyme systems. There is also scientific literature demonstrating selenium plays an important role in the humoral and cellular immune system of animals. It is interesting to note that mercury also has the ability to suppress the immune system including reducing available helper T cells and changing the helper to suppressor T cell ratios. (See Bio-Probe Vol 1, Issue 1 & 3, 1984 and Eggleston, J Prosthet Dent. 51(5):617-623, 1984).

37. AN EFFECT OF AN OCCUPATIONAL EXPOSURE TO METALLIC MERCURY ON BLOOD SERUM LEVELS OF THE SELECTED IMMUNE AND TRANSPORT PROTEINS. PRELIMINARY REPORT. SIKORSKI R. ET AL. POL TYG LEK. 41(27):855857, 1986.

Blood serum levels of the selected glycoproteins (IgG, IgM, IgA, a1AT, a2M, transfrerrin, haptoglobin, curloplasmin, C3 and C4 complement compounds) were determined in 15 women occupationally exposed to metallic mercury at the dentists' clinics and in 11 non-exposed control subjects. At the same time, total mercury in the samples of both scalp

and pubic hair of the same women was assayed. Statistically significantly lower levels of a2M were found in blood serum of the exposed women ($p < 0.005$). Total mercury was significantly higher in both the scalp and pubic hair of the exposed women in comparison to non-exposed control subjects. Reversely negative correlation of hair mercury and blood serum IgG in the exposed women was highly significant .

38. MERCURIC CHLORIDE INDUCED ANITNUCLEAR ANTIBODIES IN MICE, C.J.G.ROBINSON ET AL, TOXIC APPL PHARMACOLOGY, 1986, 86:159-169.

39. EFFECT OF METHYLPREDNISOLONE AND CYCLOPHOSPHAMIDE IN MERCURY-INDUCED AUTOIMMUNE GLOMERULONEPHRITIS. PELLETIER L PASQUIER R VIAL MC MANDET C BELAIR MF BARIETY J DRUET P NEPHROL DIAL TRANSPLANT (1987) 2(1):2-9

The effects of methylprednisolone and of cyclophosphamide were tested in mercury-induced autoimmune disease in Brown-Norway rats. Survival, proteinuria, presence of antiglomerular basement membrane bound antibodies and of immune complex type deposits, amounts of circulating immune complexes, and total serum IgE were studied. Serum IgE represents the most sensitive marker in this drug-induced autoimmune disease. Methylprednisolone alone (1.5 mg/kg per day) affected the course of the disease only slightly. Cyclophosphamide (20 mg/kg every other day) given from day 0 completely prevented all the autoimmune manifestations, but the rats were profoundly immunosuppressed. The same protective effect was obtained with lower cyclophosphamide dosage (15 mg/kg on day 0 and then 2 mg/kg per day). More interestingly, cyclophosphamide given from day 10 or 15 (20 mg/kg twice a week or every other day), at a time when the disease was already expressed, resulted in partial or complete recovery, provided that the rats had not exhibited heavy proteinuria before initiation of treatment. Cyclophosphamide is therefore a powerful agent, able to prevent and even to reduce the consequences of polyclonal activation in this model.

40. HGCL2 INDUCES NONSPECIFIC IMMUNOSUPPRESSION IN LEWIS RATS. PELLETIER L, PASQUIER R, ROSSERT J, DRUET P EUR J IMMUNOL 1987 JAN;17(1):49-54

Brown-Norway (BN) rats injected with HgCl2 have been previously shown to develop a variety of autoimmune abnormalities. The susceptibility of BN rats is genetically controlled, and Lewis rats bearing a different RT1 haplotype are resistant. It will be shown in the present study that the number of MRC OX-8+ (suppressor/cytotoxic) cells increases in the spleen and lymph nodes of Lewis rats injected with HgCl2. The responsiveness to T cell mitogens and to alloantigens is concomitantly inhibited. Spleen cells from Lewis rats injected with HgCl2 fail to induce a local graft-vs.-host reaction. Data presented show that MRC OX-8+ cells are involved in the immunosuppression in Lewis rats treated with HgCl2. Furthermore, lymph node cells and MRC OX-8+ cells from these rats are able to inhibit the normal mixed lymphocyte reaction indicating that suppression is active. Thus, HgCl2 is able to trigger immune dysregulation leading either to autoimmunity or to immunosuppression depending upon the genetic background of the rat strain tested.

41. ORAL LICHENOID REACTION RELATED TO MERCURY SENSITIVITY. JAMES J. ET AL. BR J ORAL MAXILLOFAC. SURG. 25(6): 74-480, DEC 1987.

ABSTRACT: Lichen planus is a common disorder of unknown etiology. It has been proposed that in some cases it represents a form of allergic reaction to the metals contained in dental amalgam, particularly mercury. Twenty-nine consecutive dentate patients who had lichen planus of the oral mucosa were patch-tested to the range of metals contained in dental amalgam. Ten out of 29 (34%) showed an allergic reaction to mercury and all of these patients had amalgams greater than 5 years old. The amalgams had corroded, resulting in continued release of mercury ions. Six patients had their amalgams replaced with composite or glass ionomer materials resulting in resolution of ulcerated lesions. In a follow-up of 3-24 months, one patient had a recurrence of ulcerated areas and another, despite resolution of the oral lesions had persistent discomfort.

42. Hal Huggins. Observations From The Metabolic Fringe. ICBM conf. Collarado 1988

43. Matts Hanson. Why is Mercury toxic. Basic chemical and biochemical properties of Mercury/amalgam in relation to biological effects. ICBM conference Colorado 1988

44. Autoreactive T cells in mercury-induced autoimmunity. Ability to induce the autoimmune disease. Pelltier L.; Pasquier R.; Rossert J.; Vial M.C.; Mandet C. and Druet P. J Immunol. 140(3):750-754, Feb 1988.

    ABSTRACT: It has been previously shown that autoreactive T cells appear during mercury-induced autoimmunity in Brown-Norway (BN) rats. In the present work, it is shown that: 1) T cells and T helper cells from HgCl2- injected BN rats are able to actively transfer autoimmunity in normal BN rats; the disease transferred is exacerbated when recipients are treated with the antisuppressor/cytotoxic T cell monoclonal antibody (OX8); 2) normal T cells preincubated with HgCl2 are also able to transfer the disease in OX8 -treated but not in T cell-depleted rats; and 3) T cells from HgCl2-injected BN rats also transferred the disease in both normal and T cell depleted rats. It is concluded that: 1) autoreactive T cells, and presumably anti-Ia T cells are involved in the pathogenesis of mercury- induced autoimmunity; 2) these autoreactive T cells induce suppressor/cytotoxic T cells to proliferate in normal syngeneic recipients; the fact that this T cell subset did not proliferate in HgCl2-injected BN rats suggests that HgCl2 also affects T suppressor cells; and 3) mercury- induced autoimmunity could result from the additive effect of the emergence of autoreactive T cells and of a defect at the T suppressor level.

45. Mercury induced antinuclear antibodies in mice: characterization and correlation with renal immune complex deposits. Hultman: Clin Exp Immunol (1988 Feb) 71(2):269-74

46. HULTMAN P. AND ENESTROM S. MERCURY INDUCED ANTINUCLEAR ANTIBODIES IN MICE: CHARACTERIZATION AND CORRELATION WITH RENAL IMMUNE COMPLEX DEPOSITS. CLIN EXP IMMUNOL. 71(2):269-274, FEB 1988.

BIO-PROBE REVEW:

In their introduction the authors bring up the works of other researchers who have published papers demonstrating antinuclear antibodies (ANA) as one of the hallmarks of systemic rheumatic disease in man (Tan, In: Advances in Immunology, vol 33 p. 167, 1982). ANA are also found in sera and kidneys from mouse strains with autoimmune (lupus-like) disease (Andrews et al. Spontaneous murine lupus-like syndromes. J Exp Med. 148: 1198,1978).

47. EFFECT OF MERCURIC CHLORIDE ON MICROBICIDAL ACTIVITIES OF HUMAN POLYMORPHONUCLEAR LEUKOCYTES. BAGINSKI B. TOXICOLOGY 50(3):247-256, AUG 1988.

ABSTRACT: We investigated the effects of mercuric chloride on phagocytic capacity, formation of toxic oxygen species and release of lysomal enzymes of human polymorphonuclear leukocytes (PMNL). Our results show that HgC12 may alter these microbicidal function of human PMNL without remarkable damage of cell viability. The phagocytic capacity was markedly depressed in a concentration-dependent manner. The formation of toxic oxygen species was also diminished by mercuric chloride when induced by phagocytosis. It was furthermore reduced when the PMNL were activated without phagocytosis by binding of IgG to Fc-receptors or by binding of phorbol myristate acetate to the membrane. In contrast, the release of lysosomal enzyme lysozyme was enhanced in the presence of mercuric chloride, but not the release of beta-glucoronidase. These effects may lead to impaired defense against injections and possible to inflammatory reactions in adjacent tissues induced by released lysosomal enzymes.

48. TOXICITY AND ULTRASTRUCTURAL LOCALIZATION OF MERCURIC CHLORIDE IN CULTURED MURINE MACROPHAGES. CHRISTENSEN M, MOGENSEN SC, RUNGBY J. ARCH TOXICOL. 62(6): 440-6. 1988.

The effects of mercuric chloride on cell survival, phagocytosis, and cell migration were examined in cultured mouse peritoneal macrophages, and the accumulation of mercuric chloride in the cells was visualized by autometallography and evaluated by light and electron microscopy. [Macrophages are white blood cells that ingest microorganisms or other cells and foreign particles. They are usually immobile in the walls of blood vessels or in loose connective tissues, but when stimulated by inflammation become actively mobile.] Macrophages exposed to mercury concentrations from 1.25-10 microM of mercuric chloride showed a concentration- and time-dependent increase in mercuric chloride accumulation. Cells exposed to 20 and 40 microM of mercury showed an inverse relationship between mercury concentration and the accumulation of mercury. Mercury concentrations above these levels caused cell necrosis [death]. Electro microscopy revealed that mercury was located primarily within lysosomes but also in the nucleus an cytoplasm. Mercury increased the death rate of macrophages in a concentration- dependent manner when cells were treated with mercury concentrations

not causing cell necrosis. It was also found that mercury clearly impacted macrophage random migration and possibly the capability for phagocytosis.

BIO-PROBE COMMENT:

Further clear evidence that mercury, even in very small concentrations damages the body's ability to combat foreign invaders, part of the function of the immune system.

49. MERCURY SENSITISATION INDUCED BY ENVIRONMENTAL EXPOSURE MORI T. HIRAI T. TOMIYAMA T. IIDA K., ET AL. NIPON EISEIGAKU ZASSHI. 52(4):661-666, JAN 1988

ABSTRACT: We investigated mercury sensitization in relation to urinary and hair mercury concentrations. Patch tests were performed on 215 medical students and these tests demonstrated that 28 students were mercury- sensitized (13.0%). Lifestyles were studied by questionnaire in 26 of the mercury sensitized students and 46 of the non-sensitized subjects. Urinary mercury concentrations were measure in 25 sensitized and 46 non-sensitized and hair mercury concentrations were measured in 19 sensitized and 22 non- sensitized subjects. The eating of fish was not significantly associated with mercury sensitization (one-tailed t-test). The number of teeth treated with metals in the sensitized group was significantly higher than in the control group (6.8 +/- 4.3 in sensitized vs. 4.8 +/- 4.1 in non- sensitized, one-tailed t-test p <0.05). The usage of mercurochrome was not significantly associated with mercury sensitization ((chi-squared test). Urinary mercury concentrations were not significantly higher in sensitized subjects. Hair mercury concentrations were significantly higher in sensitized subjects (1.98 +/- 0.91 micrograms/g in sensitized vs. 1.23 +/- 0.53 in non-sensitized, one-tailed t-test p <0.05). These results suggest that mercury sensitization is associated with increased hair mercury concentrations but not with urinary mercury concentrations.

50. TUMOR GROWTH-PROMOTING EFFECT OF IMMUNOSUPPRESSIVE SUBSTANCE IN MICE. FUJII M TAKAHASHI N FUJII T HAYASHI H MATSUNAGA K FURUSHO T OMURA Y YOSHIKUMI C CANCER INVEST (1989) 7(4):333-8

The effect of immunosuppressive (IS) substance obtained from cancerous ascitic fluid on tumor growth and host immunity in plasmacytoma X5563-bearing C3H/He mice is described. IS substance given in three injections, before and after tumor inoculation caused: (a) enhanced tumor growth, (b) marked reduction in survival times, (c) inhibition on Con-A response of spleen cells. Depressed natural killer (NK) activity was observed in normal and tumor-bearing mice treated with IS substance. The data presented here suggest that IS substance suppresses both humoral and cellular immunoresponsiveness and tumor cells evade immune surveillance or immunologically mediated

51. HULTMAN P SKOGH T ENESTROM S CIRCULATING AND TISSUE IMMUNE COMPLEXES IN MERCURY-TREATED MICE. IN: J CLIN LAB IMMUNOL (1989 AUG) 29(4):175-83

The amount of circulating immune complexes (CIC) was determined in mercury-treated Balb/c, SJL and C57BL/6J mice using the conglutinin- binding assay and the modified polyethylene glycol (PEG) precipitation test. SJL mice given mercuric chloride developed a transient increase of CIC by both methods, but the increase was modest compared with aged MRL-lpr/lpr (MRL) mice. Mercury-treated Balb/c mice showed increased

levels of CIC by the PEG precipitation test. Blood clearance of intravenously injected preformed soluble IC was not impaired. The mesangial IC-deposits in mercury-treated SJL mice contained significantly more IgG1, but significantly less IgG2a and C3 than the combined mesangial-capillary loop deposits in MRL mice. The MRL mice had a severe proliferative glomerulonephritis, whereas, only a mild mesangial glomerulopathy was seen in the mercury- treated SJL mice. The SJL mice given mercuric chloride showed systemic, granular deposits within the vessel walls of IgG1 but not of C3; a few mice had IgG2 deposits which were accompanied by C3. No histological damage was seen in the vessel walls. The CIC found in mercury-treated SJL and Balb/c mice may be the source of origin of the systemic IC-deposits. One explanation for the mild degree of tissue injury might be that the predominant isotype in the deposits was IgG1, which led to deposition of only small amounts of complement.

52. MIRTCHEVA J PFEIFFER C DE BRUIJN JA JACQUESMART F GLEICHMANN E IMMUNOLOGICAL ALTERATIONS INDUCIBLE BY MERCURY COMPOUNDS. III. H-2A ACTS AS AN IMMUNE RESPONSE AND H-2E AS AN IMMUNE "SUPPRESSION" LOCUS FOR HGCL2-INDUCED ANTINUCLEOLAR AUTOANTIBODIES. EUR J IMMUNOL (1989 DEC) 19(12):2257-61

In responder mouse strains repeated injections of subtoxic doses of HgCl2 induce formation of antinuclear autoantibodies (ANA) and antinucleolar autoantibodies (ANolA). Others have shown that responsiveness to HgCl2-induced formation of ANA and ANolA is linked to H-2. Here, we extend these studies to a variety of mouse strains not tested previously. After confirming that strain B10.S (H-2s) is a high responder we have shown that strains B10.D2 (H-2d) and B10.BR (H- 2k) are nonresponders. By comparing a panel of strains carrying appropriate intra-H-2 recombinant haplotypes derived from d, k and s, we were able to map responsiveness to As. Interestingly, among four strains all of which were As, and thus responsive, only the two H-2E- ones, B10.S and B10.RSD2, were high responders whereas the two H-2E+ ones, B10.HTT and B10.S(9R), were significantly less responsive. Thus, the genetics of HgCl2-induced autoantibody formation follow the rules established for immune responses to a variety of different antigens in that expression of H-2E "suppressed" the response.

53. GLEICHMANN E KIMBER I PURCHASE IF IMMUNOTOXICOLOGY: SUPPRESSIVE AND STIMULATORY EFFECTS OF DRUGS AND ENVIRONMENTAL CHEMICALS ON THE IMMUNE SYSTEM. A DISCUSSION. ARCH TOXICOL (1989) 63(4):257-73

The fundamental characteristic of the adaptive immune system which has evolved in the vertebrates is the ability to recognise, and subsequently destroy, "foreign", and potentially harmful, antigens. The selective advantage which the immune system confers is the capacity to resist infectious, and possibly malignant, disease. It has been apparent for many years that individuals in whom immune function is impaired, due either to a congenital defect or to other factors such as treatment with certain immunosuppressive drugs, exhibit an increased susceptibility to infection and, in some cases, an elevated risk of developing at least some forms of malignancy. There is an increasing awareness from rodent studies that a variety of drugs and environmental chemicals have the potential to unintentionally impair components of the immune

system. Risk assessment, based upon data from chemically induced changes in one or more parameters of immune function, is, however, dependent upon a knowledge of the functional reserve of the immune system. One of the objectives of the meeting from which this report derives was to examine what sources of information are available, and what experimental protocols can be employed, to permit accurate evaluation of immunological reserve. Although, under normal circumstances, the immune system selectively and specifically recognises foreign antigen, it is clear that the potential to recognise "self" is present and that in certain circumstances this potential is realised. Antibodies directed against normal tissue antigens have been shown to be associated with, and in some instances the presumptive cause of, "autoimmune" disease. There is a growing list of drugs and chemicals which are capable of eliciting autoantibodies and pathological autoimmune reactions. A second purpose of this meeting and of this report was to review the current state of knowledge regarding drug- and chemical-induced autoimmunity.

54. ORAL MUCOSAL LESIONS RELATED TO SILVER AMALGAM RESTORATIONS. DEPARTMENT OF ORAL BOLEWSKA-J; HANSEN-HJ; HOLMSTRUP-P; PINDBORG-JJ; STANGERUP-M ORAL- SURG-ORAL-MED-ORAL-PATHOL. 1990 JUL; 70(1): 55-8

55. DOES MERCURY FROM AMALGAM RESTORATIONS CONSTITUTE A HEALTH HAZARD? WEINER J.A., NYLANDER M. AND BERGLUND F. THE SCIENCE OF THE TOTAL ENVIRONMENT, 1990

ABSTRACT: Amalgam is the most extensively used implant material in dentistry. There have been no clinical trials of this substance and there are no epidemiological studies that allow any conclusions on the safety of amalgam fillings. Amalgam restorations continuously emit mercury vapour, which is absorbed in considerable quantities via the lungs. A comparison with dose-effect relationships, obtained in occupational studies, for certain effects on the kidneys and central nervous system (CNS), suggests that individuals with unusually high emission of mercury from amalgam fillings are at risk. It is unclear whether or not clinically significant effects could be expected. The limited sensitivity of available occupational studies, together with insufficient knowledge of possible host factors affecting resistance to mercury, implies that other more severe effects in susceptible individuals cannot be excluded. Information on long-term effects on organs other than brain or kidney is sparse. Animal studies suggest the possibility of immune system reactions t mercury, i.e. development of autoimmunity, that are not primarily dose- dependent, but rather depend o genetic susceptibility. From a toxicological point of view, amalgam is an unsuitable material for dental restorations. BIO-PROBE NOTE: This review paper will be covered in more detail in a subsequent issue.

56. SCIENTIFIC REVIEW: ELEVATED T CELL SUBPOPULATIONS IN DENTAL STUDENTS. EEDY, MB; BURROWS, D; CLIFFORD, T; FAY, A. J PROSTH DENT. 63(5):593-6. MAY 1990.

ABSTRACT: The absolute numbers of circulating white cells and lymphocyte subpopulations were studied in 25 final-year dental students and compared with a control group of 28 medical students. The total lymphocyte count, total T cell numbers

(CD3), T helper/inducer (CD4), and T suppressor/cytotoxic (CD8) numbers were significantly elevated in the dental students as compared with the control group. There was no significant difference in the T helper/inducer to T suppressor/cytotoxic cell ratios or the circulating B cell (CD21) and natural killer cell (CD16) numbers between the study and control groups. Patch testing to mercury and mercuric compounds in both the study and control groups showed no evidence of cutaneous hypersensitivity to mercury. The reason for the observed elevations in T cell subpopulations in dental students is not clear. However, one possible explanation is the dental student's occupational exposure to mercury. Further work is underway to examine this relationship and it is suggested that dental personnel take adequate measures to reduce their exposure to mercury until the results of these studies are available.

Although significant variations in T cell subpopulations were discovered, no significant elevations in total white blood cell count was found. The authors did point out that the reference range was obtained from a population of 18-65 years of age whereas the subject cohort was in ages 20- 23. The patch testing materials should also be noted. They were mercury in petrolatum (0.5%), aqueous phenyl mercuric acetate (0.01%), and 50% amalgam powder in petrolatum.

BIO-PROBE COMMENT:

This study was published in a standard dental journal with wide distribution, so its results are readily available to the dental profession. Moreover, one of its authors, Dr. Desmond Burrows, was a featured speaker at the 1984 NIDR/ADA Symposium on the Biocompatibility of Metals Used in Dentistry, thereby establishing the study's credibility in the dental community. The study presents critical information in three areas of interest:

It is clear from the study results that skin patch testing is not a valid procedure for detecting the effects of mercury on the immune system. Subjects with positive immune effects exhibited a 100% false negative response to skin patch testing with mercury and mercuric compounds.

As a result of this finding, consideration should be given to the probability that the influence o mercury on the immune system is primarily TOXIC rather than ALLERGIC (Hypersensitivity is an allergic response).

Dental authorities maintain that dentists, on the average, are healthier than the general population. Unless immune dysfunction is considered healthy, this study belies that claim. The results of this study verify previously published findings of immune dysfunction in dental students. (White & Brandt. Development of mercury hypersensitivity among dental students. JADA. 92:1204-7. 1976) (Miller et al. Prevalence of mercury hypersensitivity in dental students. J Dent Res. 64:338. Abs. # 1472. Mar 1985). It should be noted that these previous studies utilized only skin patch tests and would therefore reflect considerable false negative responses.

57. SELENIUM AND IMMUNE CELL FUNCTIONS. II. EFFECT ON LYMPHOCYTE-MEDIATED CYTOTOXICITY. ROY M KIREMIDJIAN-SCHUMACHER L WISHE HI COHEN MW STOTZKY G PROC SOC EXP BIOL MED (1990 FEB) 193(2):143-8

58. Genetic control of nickel sulfate delayed-type hypersensitivity. Ishii N., Ishii H., Ono H., Horiuchi Y., Nakajima H. and Aoki I. (1990) Journal of Investigatiue Dermatology 94, 673-676.

59. Methyl mercury exposure via placenta and milk impairs natural killer (NK) cell function in newborn rats. Ilback NG Sundberg J Oskarsson A Toxicol Lett (1991 Oct) 58(2):149-58

The effect of methyl mercury (MeHg) exposure (3.9 micrograms/g diet) on the development of immune function was studied in the newborn Sprague-Dawley rat after MeHg exposure via placenta and/or milk. No consistent alterations were observed between control and treated offspring (at the age of 15 days) on the following parameters: body weights, lymphoid organ weights or cell number, and the lymphoproliferative response to B-cell mitogen. The lymphoproliferative response to T-cell mitogen was increased in thymocytes (by 30-48%), but decreased in splenocytes (by 30-32%).

This decreased activity was only observed in the groups exposed during lactation. White blood cell counts (WBC) were increased in all groups. Natural killer (NK) cell activity was reduced (by 42%, P less than 0.01) in the group that was exposed both via placenta and milk. These results indicate that placental and lactational transfer of MeHg does adversely affect the developing immune system of the rat.

60. Effects of methyl mercury exposure on spleen and blood natural killer (NK) cell activity in the mouse. Ilback NG Toxicology (1991 Mar 25) 67(1):117-24

The effect of 12 weeks of exposure to methyl mercury (MeHg) (3.9 micrograms/g diet) on the immune function was studied in female Balb/c mice. This MeHg dose did not affect body, kidney, liver or spleen weight. Thymus weight and cell number decreased by 22% (P less than 0.05) and 50% (P less than 0.001), respectively. The lymphoproliferative response to T and B cell mitogens, however, tended to increase in both lymphoid organs. Natural killer cell activity was reduced by 44% (P less than 0.01) and 75% (P less than 0.05) in the spleen and blood, respectively. The number of red blood cells increased slightly (12%, P less than 0.05), whereas white blood cell counts were unaffected. These results indicate that MeHg evokes immune suppressive effects on protective cytotoxic capacity that is of major importance in the pathogenesis of several diseases.

61. Effects of amalgam on cells of the immune system . Wilhelm-M; Dunninger-P; Ruppel-R; Tony-HP; Wilms-K; Klaiber-B Med. Poliklinik der Universitat, Wurzburg. Dtsch-Zahnarztl-Z. 1991 Aug; 46(8): 544-7 1991

62. Strain differences in the effect of mercury on murine cell-mediated immune reactions. Hultman P, Johansson U (1991) Food and Chemical Toxicology, 29(9): 633– 638.

The effect of mercuric chloride on mitogen-induced DNA synthesis was investigated using lymphocytes from SJL and DBA mice, which are known to be susceptible and resistant to induction of autoimmunity by mercury, respectively. Treatment of SJL mice with 5 ppm mercuric chloride in their drinking-water for 2 wk resulted in a two- to three-fold increase of concanavalin A and lipopolysaccharide-induced thymidine incorporation in splenocytes. Mitogen-induced thymidine incorporation in splenocytes from identically treated DBA mice was not significantly different from that seen in controls. In

vitro treatment of splenocytes from SJL mice with mercury caused a dose-dependent increase of concanavalin A-, lipopolysaccharide and phytohaemagglutinin-induced thymidine incorporation. This effect was optimal when 10(-7)-10(-8) M-mercuric chloride were added as a pulse 1 hr before the addition of mitogens, whereas higher and lower concentrations were less effective. The mitogen-induced DNA synthesis in splenocytes from DBA mice was either not affected by the addition of mercuric chloride or decreased by higher mercury concentrations. The addition of mercury to thymocytes from DBA and SJL mice caused a slight and moderate increase, respectively, in concanavalin A-induced thymidine incorporation.

63. Evaluating the Systemic Immune Response to Mercury Compounds Stejfkal V; International Academy of Oral Medicine and Toxicology Annual Scientific Session Seattle, Wash 9/1991

64. Effects of amalgam on cells of the immune system Wilhelm: Dtsch Zahnarztl Z (1991 Aug) 46(8):544-7

65. Metals in plasma and cerebrospinal fluid in normal aging and Alzheimer's disease, H.Basun et al, J Neural Transm Park Dis Dement Sect, 1991,3(4):231-58

66. Beeinflubung der zellularen Immunabwehr drch Quecksilberfreisetzung, W.Kostler, Forum Prakt. Allgem. Arzt, 1991, 30(2):62-3

67. Benefiecial effect of human therapeutic IV-Ig in mercury indueced autoimune disease Cossi et al, Clin Exp Immunol, Apr, 1991

68. Chemically induced autoimmunity ..., M.Goldman et al,1991,"Immunology Today,12:223

69. Comprehensive medical examination of a group of patients with alleged adverse effects from dental amalgams. Anneroth-G; Ericson-T; Johansson-I; Mornstad-H; Ryberg-M; Skoglund-A; Stegmayr-B Acta-Odontol-Scand. 1992 Apr; 50(2): 101-11 1992

70. Immunotoxic effects of mercuric compounds on human lymphocytes and monocytes:Alterations in cell viability" B.J. Shenker et al, Dept. Of Pathology,Univ. Of Penn. School of Dental Med.,"Immunopharmacologicol Immunotoxical, 1992, 14(3):555-77;

71. Immune suppression of human T-cell activation, Immunopharmacologicol Immunotoxical, B.J. Shenker et al 1992, 14(3):555-77, & 14(3):539-53; & 1993, 15(2-3):273-90;

72. Failure to detect any effect of amalgam restorations on peripheral blood lymphocyte populations. Wilhelm M Dunninger P Ruppel R Tony HP Wilms K Klaiber B Clin Investig (1992 Sep) 70(9):728-34

Dental amalgam has been considered to have adverse side effects on the immune system. Reports have been contradictory, indicating both an increase and a decrease in peripheral blood lymphocyte counts associated with amalgam restorations. We investigated two groups of patients, one of which was treated with amalgam restorations for the first time. In the other group, all existing amalgam fillings were removed. Prior to and after treatment, we determined the absolute and relative numbers of granulocytes, lymphocytes, monocytes, T cells, B cells, cytotoxic T cells, helper T cells and natural killer cells. In addition, functional investigations of T cells were performed. We failed to find any effect of amalgam restorations on the immune system in terms of the parameters investigated.

73. Murine susceptibility to mercury. I. Autoantibody profiles and systemic immune deposits in inbred, congenic, and intra-H-2 recombinant strains. Hultman P, Bell LJ, Enestrom S, Pollard KM Clin Immunol Immunopathol 1992 Nov;65(2):98-109

Inbred, congenic, and intra-H-2-recombinant mouse strains were given subcutaneous injections of either 1.6 mg HgCl2/kg body wt or 0.1 ml NaCl thrice weekly for 5-6 weeks. Mercury-treated mice from strains carrying the H-2s haplotype developed antinucleolar antibodies (ANoA), which targeted the 34-kDa nucleolar protein fibrillarin, and in some instances also nucleolar proteins of 60-70 and 10-15 kDa, the latter corresponding to histones. Strains with H-2b and H-2d haplotypes were resistant to induction of ANoA. The susceptibility to development of AnoA/antifibrillarin antibodies (AFA) was mapped to the H-2A-region using intra-H-2-recombinant strains. We were not able to confirm earlier reports that expression of H-2E genes dampens the development of ANoA. Mercury treatment caused a substantial increase in the titer of antichromatin (ACA) and/or antihistone (AHA) antibodies in a fraction of SJL/J, A.SW, A.TH, B10.S, and B10.HTT mice (H-2s), and in A/J (H-2k) mice, whereas mice from the C57BL/6J and C57BL/10J (H-2b), and the DBA and BALB/c (H-2d) strains were low or nonresponders. The development of AHA and ACA could not be linked to the H-2 complex. A significant, substantial increase of granular mesangial and systemic vessel wall IgG deposits occurred in mice with serum ANoA/AFA. However, the B10.S(9R) and B10.HTT strains, which express the H-2E genes, developed only an intermediately increased titer of mesangial IgG deposits. Systemic vessel wall IgG deposits occurred in only 60-80% of the B10.S(9R) mice and in none of the B10.HTT mice. This contrasted with the high titer of mesangial IgG deposits and uniform development of systemic vessel wall IgG deposits observed in B10.S mice not expressing H-2E. Mice with mesangial IgG deposits showed a mild glomerulonephritis. There was no systemic vasculitis. The susceptibility to development of ANoA, AHA, ACA, and systemic, granular IgG deposits in the B10.S strain was influenced by the sex, since males showed less uniform development of these immunopathologic features than females.

74. Dose-response studies in murine mercury-induced autoimmunity and immune- complex disease. Hultman P, Enestrom S Toxicol Appl Pharmacol 1992 Apr;113(2):199-208

    Female SJL/N mice were given either 5.0, 2.5, 1.25, or 0.625 mg mercuric chloride per liter drinking water (ppm HgCl2). Serum antinucleolar antibodies (ANuA) of the IgG class were seen in mice given at least 1.25 ppm HgCl2 for 10 weeks, a dose which corresponded to a mean renal mercury concentration, as measured with atomic absorption spectrophotometry, of 2. 4 +/- 0.43 microgram Hg/g wet weight (ppm Hg; means +/- 1 SD). At a dose of 5.0 ppm HgCl2 all mice showed IgG ANuA with a mean titer of 1:846 and a mean renal mercury concentration of 14.8 +/- 3.9 ppm. Significantly increased titers of granular IgG deposits, corresponding to immune-complex (IC) deposits, developed in the renal mesangium of mice given 5.0 ppm HgCl2. Mice with heavy mesangial IgG deposits showed a mild glomerular endocapillary cell proliferation and widening of the mesangium. Renal vessel wall IgG deposits were found only in mice given 5.0 ppm HgCl2, whereas such deposits were seen in splenic and cardiac arteries of mice receiving 1.25 ppm or more of HgCl2. The renal and splenic mercury concentration was significantly increased in all groups of mercuric chloride-exposed mice and correlated with the dose. We conclude that 10 weeks peroral treatment with mercuric chloride in drinking water is able to elicit autoimmunity and IC disease in genetically homogeneous, mercury- sensitive mice at a body burden similar to that reported in some occupationally exposed humans.

75. Resolution of oral lichenoid lesions after replacement of amalgam restorations in patients allergic to mercury compounds. Laine J Kalimo K Forssell H Happonen RP Br J Dermatol (1992 Jan) 126(1):10

76. Murine susceptibility to mercury. II. autoantibody profiles and renal immune deposits in hybrid, backcross, and H-2d congenic mice. Hultman Clin Immunol Immunopathol (1993 Jul) 68(1):9-20

77. Minor effects of low exposure to inorganic mercury on the human immune system. Langworth S Elinder CG Sundqvist KG Scand J Work Environ Health (1993 Dec) 19(6):405-13

78. Comparision of interaction of meHgCl2 and HgCl2 with murine macrophages, M.M. Christensen et al, Institute of Medical Microbiology, Arch Toxicol, 1993, 67(3):205-11;

79. Murine susceptibility to mercury. II. autoantibody profiles and renal immune deposits in hybrid, backcross, and H-2d congenic mice. Hultman P, Bell LJ, Enestrom S, Pollard KM Clin Immunol Immunopathol 1993 Jul;68(1):9-20

    Inorganic mercury causes systemic autoimmunity and/or immune-complex deposits in strains of mice carrying certain H-2 haplotypes, for example H- 2s and H-2d. This study aimed at describing the genetic mechanisms regulating these reactions. Inbred SJL, C57BL/6J (B6), C57BL/10J (B10), and DBA mice, F1(SJL x DBA), F1(SJL x B6), and F2(SJL x

B6) hybrids, and mice derived from a backcross of SJL or B6 mice to F1(SJL x B6) hybrids were given subcutaneous injections of either 1.6 mg HgCl2/kg body wt or 0. 1 ml NaCl every third day for 6 weeks. SJL mice developed a high titer of serum antinucleolar antibodies (ANoA) of the IgG class targeting the nucleolar protein fibrillarin and a significantly increased titer of IgG and C3 colocalized as granular deposits in the renal mesangium and vessel walls. The B6 and DBA strains lacked ANoA and showed no increase in titers of immune deposits. Nine percent of mercury-treated F1(SJL x DBA) hybrids developed IgG-ANoA which were of a low titer, and only occasional hybrids showed an increased titer of granular mesangial IgG deposits. Mercury treatment induced ANoA of low titer in 41% of F1(SJL x B6) hybrids, and 24% had increased granular mesangial immune deposits. Four of 61 mercury- treated BC-[SJL x F1(SJL x B6)] mice showed ANoA which were of a high titer and targeted the nucleolar protein fibrillarin. ANoA were not found in 55 mercury-treated F2(SJL x B6) hybrids or in 56 mercury-treated mice derived from a backcross of B6 mice to F1(SJL x B6) hybrids. Increased mesangial immune deposits were regularly accompanied by vessel wall deposits in F1- and F2(SJL x B6) hybrids, but only 53% of BC(SJL x F1[SJL x B6]) mice with increased mesangial deposits had vessel wall deposits. Vessel wall immune deposits were only present in mice with increased mesangial deposits. A majority of mice which developed significantly increased titers of mesangial IC deposits showed no ANoA. In conclusion, the susceptibility in SJL mice to develop ANoA during mercury treatment, which has been shown to reside in the H-2A locus, was codominantly inherited in a cross with mice carrying the H-2b and H2d haplotypes. Non-H- 2 genes dampened ANoA expression to a degree which varied between the strains. Since renal vessel and mesangial IC deposits developed in backcross mice lacking serum ANoA, these deposits must contain IC not related to fibrillarin-antifibrillarin.

80. The Influence of Amalgam on Immune Response of Gum Tissues. Prajitno, M. J Dent Research. (1994, Apr): 73(4), 1013, A-15.

81. MELISA: tool for the study of metal allergy, VDM Stejskal et al, Toxicology in Vitro, 8(5):991-1000, 1994.

82. Immunoglobulin Levels in Workers Exposed to Inorganic Mercury, M.L.S.Queiroz et al, Pharmacol Toxicol 74:72-75, 1994;

83. Polymorphonuclear phagentosis in workers exposed to mercuryvapor, R.C.Perlingeiro et al, Int J Immounopharmacology", 16(12):1011- 7,1994;

84. Healing of lichenoid reactions following removal of of amalgam. A clinical follow-up. Henriksson E Mattsson U Hakansson J J Clin Periodontol (1995 Apr) 22(4):287-94

85. Resolution of lichen planus following removal of amalgam restorations in patients with proven allergy to mercury salts: a pilot study. Smart ER Macleod RI Lawrence CM Br Dent J (1995 Feb 11) 178(3):108-12

86. Does amalgam affect the immune system? A controversial issue. Enestrom S Hultman P Int Arch Allergy Immunol (1995 Mar) 106(3):180-203

87. "Mercury: god of TH2 cells", P.W. Mathieson, 1995, Clinical Exp Immunol.,102(2):229-30

88. Three cases of linear lichen planus caused by dental metal compounds. Sasaki G, Yokozeki H, Katayama I, Nishioka K J Dermatol 1996 Dec 23:12 890- 2

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53 patients with complaints which they attributed to their amalgam fillings, and with pathological tests indicating abnormality of the immune system, were followed for 1-3 years after the removal of all, part of, or none of their amalgam fillings. Within the group of 34 individuals who had all their amalgam fillings replaced, there was a significant number of decreased antibody titres, but only two had normalised their laboratory tests after 1-3 years. A significant improvement in subjective symptoms occurred in 20 (59%) of cases. In the group of patients who still had amalgam fillings, there were no statistically significant changes in the antibody titres. It thus seems that mercury released from amalgam fillings may initiate or support an ongoing immune disease. However. this study group was rather heterogeneous, and had received various pharmacological treatments. Further studies, are, therefore, needed to confirm, or refute, the results.

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97. Mercury-specific lymphocytes: an indication of mercury allergy in man. Stejskal VD Forsbeck M Cederbrant KE Asteman O J Clin Immunol (1996 Jan) 16(1):31-40

98. Immunoglubuline E in mercury exposed workers, D.C.Santos, 1997, 19(3):383-92.

99. MATERIAL SAFETY DATA SHEET for Dispersaloy made by Caulk 1997

Inhalation: Chronic Inhalation of mercury vapor over a long period may cause mercurialism which is characterized by fine tremors and erethism. Tremors may affect the hands first, but may also become evident in the face, arms, and legs. Erethism may be manifested by abnormal shyness, blushing, self-consciousness, depression or despondency resentment of criticism, irritability or excitability, headache, fatigue, and insomnia. In severe cases, hallucinations, loss of memory, and mental deterioration may occur. Concentrations as low and 0.03 mg/m ^{3} have induced psychiatric symptoms in humans. Renal involvement may be indicated by proteinuria, albuminuria, enzymuria, and anuria. Other effects may include salivation, gingivitis, stomatitis, loosening of the teeth, blue lines on the gums, diarrhea, chronic pneumonitis and mild anemia. Repeated exposure to mercury and its compounds may result in sensitization. Intrauterine exposure may result in tremors and involuntary movements in the infants. Mercury is excreted in breast milk. Paternal reproductive effects and effects on fertility have been reported in male rats following repeated inhalation exposures. First Aid Remove from exposure area to fresh air immediately. If breathing has stopped, give artificial respiration. Maintain airway and blood pressure and administer oxygen if available. Keep affected person warm and at rest. Treat symptomatically and supportively. Administration of oxygen should be performed by qualified personnel. Get medical attention immediately.

100. German Scientists Reveal Mercury Amalgam Affects

Toxic Materials and Infertility: Heavy Metals and Minerals. Gerhard, I; Runnebaum, B. Obstetrics Gynaecology. 52:383-96. 1992. Diagnosis of Heavy Metal Loading by the Oral DMPS and chewing gum tests. Gerhard I: Waldbrenner P; Thuro H; Runnebaum B. Clinical Lab. 38: 404-11 . 1992

101. Human Fertility. In a cell culture experiment, mercury affected hormone production at low concentrations.

A link has been found between mercury and hormone disturbances, immune disturbances, recurrent fungal infections, hair loss and allergies. The differences are large. Allergies and hair loss are 2-3 times as common in the high-mercury group. These recent results confirm earlier findings from Heidelberg on mercury and fertility. According to the researchers, mercury exposure leads to hormone and immune disturbances that can reduce fertility.

In a cell culture experiment at the Tuebingen University gynecological clinic, mercury affected hormone production at low concentrations. The concentrations were so low that cell vitality was otherwise almost unaffected.

Professor Ingrid Gerhard and her co-workers and the university gynecological clinic in Heidelberg have examined more than 1000 patients for mercury, fertility problems and symptoms. Mercury was measured after giving a so-called chelating agent known as DMPS. This substance mobilizes mercury from tissues, particularly the kidneys, so that it is excreted in the urine where it can be measured.

The high-mercury group had more hormonal disturbances, immune disturbances, recurring fungal infections, hair loss and allergies. A number of different hormonal disturbances were found, sex hormones among them. All these differences were statistically significant and some very marked. Allergies and hair loss were 2-3 times more common in the high-mercury group. The doctors at the clinic have successfully treated fertility problems with a combination of vitamins/minerals and amalgam removal. According to professor Gerhard, mercury exposure leads to hormone and immune disturbances that can reduce fertility.

102. MURINE SYSTEMIC AUTOIMMUNE DISEASE INDUCED BY MERCURIC CHLORIDE (HGCL2): HG-SPECIFIC HELPER T-CELLS REACT TO ANTIGEN STORED IN MACROPHAGES. KUBICKA-MURANYI M BEHMER O UHRBERG M KLONOWSKI H BISTER J GLEICHMANN E INT J IMMUNOPHARMACOL (1993 FEB) 15(2):151-61

The adoptive transfer popliteal lymph node assay (PLNA) was used to demonstrate Hg-specific T-cell responses of mice that were continuously treated with HgCl2 by a regimen known to induce a systemic autoimmune disease in H-2s (murine histocompatibility complex, haplotype s) mice, but not H-2d mice. We found that spleen cells of B10.S and A.SW donors (both H-2s) responded anamnestically to HgCl2 by inducing a significant increase in cellularity in the draining PLN of the recipient: In contrast, spleen cells of HgCl2- treated DBA/2 (H-2d) donors failed to induce an increase in PLN cellularity, and spleen cells of B10.D2/n (H-2d) donors induced no changes or even diminished PLN cellularity upon re-encounter with HgCl2. Kinetic studies showed that spleen cells of B10.S donors were stimulatory from day 3 until day 14 of donor HgCl2 treatment and, when purified splenic T-cells were tested, still on day 28, the last point in time tested. The Hg-specific T-cells prepared from HgCl2- treated B10.S mice not only induced an increased cellularity, but also B-cell activation to antibody secretion in the draining PLN of the recipient. Moreover, the Hg-specific donor T-cells transferred could specifically be restimulated by killed peritoneal cells obtained from the same donors or from syngeneic donors previously treated with HgCl2. Interestingly, when killed peritoneal cells were injected as antigen the amount of Hg required for T-cell restimulation was only 1/40 of that required when free HgCl2 was used. Taken together, these results show that an HgCl2 treatment schedule designed to induce systemic autoimmune disease primes Hg-specific T-helper (Th) cells and generates immunogenic material in peritoneal cells to which the T-cells react. The possible contribution to the pathogenesis of HgCl2-induced auto-immune disease of these Hg-specific T-cells and the autoreactive T-cells reported in the literature is discussed.

103. AUTOIMMUNITY AND HEAVY METALS. BIGAZZI PE LUPUS (1994 DEC) 3(6):449-53

This brief review is focused on those heavy metals (cadmium, gold and mercury) that have strong associations with autoimmunity. Cadmium treatment of rats and mice

results in autoimmune responses that vary with species and inbred strain of animals. However, there is no solid evidence demonstrating that the renal pathology observed in humans exposed to cadmium has an autoimmune pathogenesis. More clear-cut are the autoimmune effects of preparations containing gold salts, that have been widely used in the treatment of rheumatoid arthritis. Gold may cause autoimmune thrombocytopenia, immune complex-mediated glomerulonephritis and other autoimmune disorders. Similarly, there is solid evidence that mercury can induce autoimmune disease both in humans and experimental animals. The lessons to be derived from metal-induced autoimmunity relate to structure-activity relationship, pathogenesis, etiology and genetics. They probably apply to xenobiotic-induced autoimmune disease in general.

104. ROLE OF MERCURY (HG) IN RESISTANT INFECTIONS & EFFECTIVE TREATMENT OF CHLAMYDIA TRACHOMATIS AND HERPES FAMILY VIRAL INFECTIONS (AND POTENTIAL TREATMENT FOR CANCER) BY REMOVING LOCALIZED HG DEPOSITS WITH CHINESE PARSLEY AND DELIVERING EFFECTIVE ANTIBIOTICS USING VARIOUS DRUG UPTAKE ENHANCEMENT METHODS. OMURA, Y; BECKMAN, SL. ACUPUNCT ELECTROTHER RES, 20(3-4):195-229,1995.

ABSTRACT: The authors found that antibiotics used to treat various infections often were ineffective in the presence of abnormal localized deposits of heavy metals like Hg and Pb, which were often observed to co- exist with Chlamydia trachomatis, Herpes Simplex Types I & II, Cytomegalovirus (CMV), and other micro-organisms.

Our earlier research revealed that despite rigorous treatment with antibiotics together with various drug uptake enhancement techniques, subjects who had been treated for Chlamydia trachomatis infections, seemingly successfully with disappearance of their symptoms, were often experiencing recurrences within several months after completion of their treatment despite taking precautions against reinfection. Careful examination of the entire body of these symptom-free patients with the BiDigital O-Ring Test revealed that the Chlamydia trachomatis had retreated to 3 of approximately 5 hiding places with localized increase in uric acid levels: 1) sublingual caruncle, 2) a small round area in the right and/or left axillae, 3) the genitals (Corona Glandis area of the Glans Penis at the Fossa Navicularis of the urethra in the male, and near the orifice of the urethra in the female), 4) Insulin-like Growth Factor positive horizontal lines, particularly above and below the knees, 5) the maxillary, ethmoid and frontal sinuses and the horizontal lines at the base of the nostrils (particularly small areas where Insulin-like Growth Factors exist). We found that all these areas contain Insulin-like Growth Factors I & II which are reduced in the presence of infection.

Even when drug uptake of antibiotics was selectively increased in these 3 of approximately 5 areas by various drug uptake enhancement methods developed by the 1st author, still the infection persisted. In the spring of 1995, use of Chinese parsley for successful elimination of Hg deposits existing in various organs of the first author as the result of the decay of radioactive Thallium 201 injected for cardiac SPECT, was accidentally discovered after eating Vietnamese soup, which happened to contain Chinese parsley, also called cilantro. We also found Chinese parsley accelerates the excretion of Hg, Pb, and Al from the body through the urine.

Our subjects were given a course of antibiotics (Doxycycline for Chlamydia trachomatis infection) or anti-viral agents (EPA with DHA for Herpes Family Viruses) together with

Chinese parsley. Since these vegetable/herbs were eaten, the amount of effective substance
absorbed varied and some people did not like the taste of these relatively large amounts of either cooked or raw parsley or its juice, but together with effective antibiotics delivered by drug uptake enhancement methods to the infected areas, the substances worked synergistically, rapidly reducing the generalized symptoms and infection.
The micro-organisms retreated to the 3 approximately 5 areas listed above where, with continued treatment, they were significantly reduced, but not completely eliminated. Because of these problems, a pharmaceutical company was asked to produce a Chinese parsley tablet containing a controlled amount in a highly absorbable form.
When 11 subjects were treated with Doxycycline for Chlamydia trachomatis infection, or anti-viral agents (EPA with DHA) for Herpes Family Viruses, drug uptake enhancement methods to selectively increase delivery of the drugs to the affected areas, and Chinese parsley tablets to remove the heavy metal deposits, the last traces of the infections and clinical symptoms disappeared completely.
Therefore we hypothesized that the infectious microorganisms mentioned above, somehow utilize the Hg or Pb to protect themselves from what would otherwise be effective antibiotics, and/or that heavy metal deposits in some way make antibiotics ineffective. Since the microorganisms retreat to areas in which Insulin-like Growth Factors I & II normally exist, they may be utilizing them for their own growth and multiplication.

105. NEW ASPECTS OF MURINE COXSACKIE B3 MYOCARDITIS--FOCUS ON HEAVY METALS. ILBACK, NG; LINDH, U; FOHLMAN, J; FRIMAN, G. EUR HEART J, 16(SUPPL 0):20-4, 1995.

ABSTRACT: The magnitude of inflammatory lesions in the hearts of coxsackie B3 (CB3)-virus infected mice can be affected by the potentially toxic heavy metals cadmium (Cd), nickel (Ni) and methyl mercury (MeHg). The infection is associated with a changed distribution, such as Cd accumulation in the spleen and kidneys. New target organs for Ni during the infection were the heart, pancreas and lungs in which inflammatory lesions were present. This increased uptake was correlated with the disturbed function of immune cells and an increased inflammatory reaction.
Ni and MeHg appeared to have a direct effect on immune cells that resulted in changed natural killer cell activity and decreased mobilization of macrophages, CD4+ and CD8+ cells into the inflammatory lesions.
Although MeHg increased spleen T cell activity and gamma-interferon (IFN- gamma) levels, the inflammatory lesions in the heart increased. Another detrimental effect of MeHg treatment was evident by an increased calcium and decreased zinc content in the inflamed heart, which may partly explain the more severe inflammatory lesion. The host's response, CB3 infection, changed the distribution of each metal in a specific way, a fact which may subsequently result in altered target organ toxicity and resistance to the infection.

106. IMMUNE THROMBOCYTOPENIA AND ELEMENTAL MERCURY POISONING. FOURTES, LJ; WEISMANN, DN; GRAEFF, ML; BALE, JF, JR; TANNOUS, R; PETERS, C. J TOXICOL CLIN TOXICOL., 33(5):449-55, 1995.

ABSTRACT:

Three cases of severe mercury toxicity occurring within a family are reported. Two cases of thrombocytopenia occurred in this family and represent the second such report in the literature of an association between elemental mercury toxicity and thrombocytopenia. Three of the children presented with a combination of dermatologic and neurologic manifestations reminiscent of acrodynia or pink disease. Each of the four children in this family were treated with dimercaptosuccinic acid. The hazard of vacuuming spilled mercury and appropriate clean-up procedures are described.

107. MURINE GENOTYPE INFLUENCES THE SPECIFICITY, MAGNITUDE AND PERSISTENCE OF MURINE MERCURY-INDUCED AUTOIMMUNITY. HULTMAN P TURLEY SJ ENESTROM S LINDH U POLLARD KM J AUTOIMMUN (1996 APR) 9(2):139-49

Genetic factors are major contributors in determining the susceptibility to systemic autoimmune diseases. We studied the influence of genotype on systemic autoimmunity by treating female

mice of the H-2s strains SJL/N, SJL/J, A.SW, and B10.S with mercuric chloride (HgCl2) for 10 weeks and then following autoantibody and tissue immune deposits during the subsequent 12 months. All strains developed antinucleolar antibodies (ANoA) of the IgG class which reacted in immunoblotting with a 34-kDa nucleolar protein identified as fibrillarin. The titre of ANoA attained after 10 weeks' treatment varied from 1:1,280 to 1:20,480 in the order: A.SW > SJL > > B10.S. Following cessation of HgCl2 treatment ANoA and antifibrillarin antibodies (AFA) persisted for up to 12 months, although some B10.S mice showed pronounced reduction not only of their autoantibody titres, but also systemic immune deposits when compared to other H-2s strains. A second set of autoantibodies targeted chromatin and in some mice specifically histones, and were distinguished from the ANoA by a rapid decline after treatment and a susceptibility linked to the non-H-2 genes of the SJL. Tissue levels of mercury remained elevated above untreated controls throughout the study period, suggesting that the mercury detected in lymphoid tissues may provide stimulation of lymphoid cells specific for fibrillarin for a considerable period after exposure has ceased. We conclude that H-2 as well as non-H-2 genetic factors distinctly influence not only the susceptibility to induction of autoimmunity, but also the specificity and magnitude of the response.

108. AMALGAM MERCURY - EMERGING EVIDENCE QUESTIONS A DENTAL PARADIGM. (LORSCHEIDER ET AL. FASEB J., 7:1432-1433, 1993).

ABSTRACT: The use of mercury (Hg) metal as a material component in dental tooth fillings began in the early 1800's, and since its introduction periodic concerns have arisen about the health safety risks to dentists and their patients. For over 160 years the opinion within dentistry has been that Hg remains "locked in' the alloy portion of the amalgam fillings, a belief not based upon experimental evidence. At the present time amalgam fillings contain approximately 50 % Hg and are used for 80% or more of all tooth restorations.

Since 1980 several laboratories have demonstrated that dental amalgam continuously releases Hg vapour (Hg°@ into human mouth air. Intra-oral air concentration of Hg° is

correlated with the number of occlusal amalgam fillings in molar teeth. A primary absorption route is via respiration, where 80@ of inhaled Hg) can be retained in somatic cells where it is typical]y oxidised to Hg2+ and co-valently bound to proteins.

Combinations of animal and human experiments conducted over the past decade have demonstrated significant body uptake, distribution and excretion of amalgam Hg. Based upon accumulated evidence, there is MOW general concurrence within medical science that the largest contributor to Hg body burden is dental amalgam Recent studies have examined possible systemic pathophysiological effects of amalgam Hg. Current research directions worldwide include investigations of: induction of antibiotic resistance in Hg-resistant intestinal bacteria, suppression of several indices of immune function, impaired kidney f unction, inter-tility, and alterations of specific brain neurochemistry. The collective results of such studies do not support the notion of amalgam safety, but instead bring into question the continued use of Hg within dentistry, and thus strongly contradict the opinions officered by various dental associations and related trade organiza-tions that the safety of amalgams is assured because of their popularity and long-term use

109. IMMUNOTOXICOLOGY OF CADMIUM AND MERCURY ON B-LYMPHOCYTES--I. EFFECTS ON LYMPHOCYTE FUNCTION. DAUM JR SHEPHERD DM NOELLE RJ INT J IMMUNOPHARMACOL (1993 APR) 15(3):383-94

Heavy metals have been shown to exert immunotoxic effects on humoral immunity. To ascertain the mechanisms by which these immunotoxic effects are exerted, the effects of CdCl2 and HgCl2 on the biology of murine B-lymphocytes were studied. It was shown that CdCl2 and HgCl2 inhibited B-cell RNA and DNA synthesis. The IC50 (the concentration required to inhibit a specific B-cell function by 50%) for CdCl2 was 30 microM for RNA synthesis and DNA synthesis. The IC50 for HgCl2 was 50 and 120 nM for RNA and DNA synthesis, respectively. Cell cycle analysis revealed that B-cells were arrested throughout the cell cycle with CdCl2 and HgCl2. The inhibitory effects exerted by CdCl2 and HgCl2 were rapid, inhibiting RNA synthesis within 2 h of activation. Differentiation to Ig secretion was inhibited by CdCl2 and HgCl2 in culture and there appeared to be selective effects on specific Ig isotypes. IgG3 production was most sensitive to inhibition by CdCl2 and HgCl2 followed by IgG1 and IgG2b and then IgM and IgG2a. Changes in the expression of B-cell surface antigens induced by LPS were also influenced by CdCl2. LPS-induced increases in class II MHC expression was inhibited by CdCl2, as was the constitutive expression of class I MHC antigen. A summary of the IC50 for CdCl2 and HgCl2 are presented. In summary, both CdCl2 and HgCl2 exert early, inhibitory effects on B-cell activation. This is manifested by the inhibition of RNA, DNA and antibody synthesis. However, selective effects on the production of specific Ig isotypes by these metals may influence the ability of B-cells to mount effective immune responses to pathogens.

110. MURINE SYSTEMIC AUTOIMMUNE DISEASE INDUCED BY MERCURIC CHLORIDE (HGCL2): HG-SPECIFIC HELPER T-CELLS REACT TO ANTIGEN STORED IN MACROPHAGES. KUBICKA-MURANYI M BEHMER O UHRBERG M KLONOWSKI H BISTER J GLEICHMANN E INT J IMMUNOPHARMACOL (1993 FEB) 15(2):151-61

The adoptive transfer popliteal lymph node assay (PLNA) was used to demonstrate Hg-specific T-cell responses of mice that were continuously treated with HgCl2 by a regimen

known to induce a systemic autoimmune disease in H-2s (murine histocompatibility complex, haplotype s) mice, but not H-2d mice. We found that spleen cells of B10.S and A.SW donors (both H-2s) responded anamnestically to HgCl2 by inducing a significant increase in cellularity in the draining PLN of the recipient: In contrast, spleen cells of HgCl2- treated DBA/2 (H-2d) donors failed to induce an increase in PLN cellularity, and spleen cells of B10.D2/n (H-2d) donors induced no changes or even diminished PLN cellularity upon re-encounter with HgCl2. Kinetic studies showed that spleen cells of B10.S donors were stimulatory from day 3 until day 14 of donor HgCl2 treatment and, when purified splenic T-cells were tested, still on day 28, the last point in time tested. The Hg-specific T-cells prepared from HgCl2- treated B10.S mice not only induced an increased cellularity, but also B-cell activation to antibody secretion in the draining PLN of the recipient. Moreover, the Hg-specific donor T-cells transferred could specifically be restimulated by killed peritoneal cells obtained from the same donors or from syngeneic donors previously treated with HgCl2. Interestingly, when killed peritoneal cells were injected as antigen the amount of Hg required for T-cell restimulation was only 1/40 of that required when free HgCl2 was used. Taken together, these results show that an HgCl2 treatment schedule designed to induce systemic autoimmune disease primes Hg- specific T-helper (Th) cells and generates immunogenic material in peritoneal cells to which the T-cells react. The possible contribution to the pathogenesis of HgCl2-induced auto-immune disease of these Hg-specific T-cells and the autoreactive T-cells reported in the literature is discussed.

111. Adverse Immunological Effects and Autoimmunity Induced by Dental Amalgam and Alloy in Mice. Hultman, P; Johansson, U; Turley, SJ; Lindh, U; Enestrom, S; Pollard, KM. FASEB J. (1994): 8, 1 183-1190.

112. ADVERSE IMMUNE EFFECTS OF DENTAL AMALGAM - NEW EVIDENCE!

The following abstract is from a study published in the November 1994 issue of the FASEB Journal (Vol. 8, Pgs. 1183-1190). The study was conducted at three medical research centers. two in Sweden and one in the United States (The Scripps Research Institute, La Jolla, California, and demonstrated that both mercury and silver from dental amalgam adversely effects the immune system in genetically susceptible animals.

ABSTRACT: Dental amalgam fillings are the most important source of mercury exposure in the general population, but their potential to cause systemic health consequences is disputed. In this study. inbred mice genetically susceptible to mercury-induced immune aberrations were used to examine whether dental amalgam may interfere with the immune system and cause autoimmunity.

Female SJL/N mice were implanted in the peritoneal cavity with 8-100 mg silver amalgam or silver alloy for 10 weeks or 6 months. Chronic hyperimmunoglobulinemia serum IgG autoantibodies targeting the nucleolar protein fibrillarin, and systemic immune-complex deposits developed in a time- and dose-dependent manner after implantation of amalgam or alloy. Splenocytes from mice implanted with amalgam or alloy showed an increased expression of class II molecules. The functional capacity of splenic T and B cells was affected in a dose-dependent way: 10 weeks of low-dose and 6 months of high-dose amalgam implantation strongly increased mitogen- induced T and B cell proliferation, whereas 10 weeks of high-dose implantation decreased the proliferation.

Not only mercury but also silver accumulated in the spleen and kidneys after amalgam implantation. In conclusion, dental amalgam implantation in a physiological body milieu causes chronic stimulation of the immune system with induction of systemic

autoimmunity in genetically sensitive mice. Implantation of silver alloy not containing mercury also induced autoimmunity, suggesting that other elements, especially silver, have the potential to induce autoimmunity in genetically susceptible vertebrates.
Accumulation of heavy metals, from dental amalgam and other sources, may lower the threshold of an individual] metal to elicit imunological aberrations. We hypothesise that under appropriate conditions of genetic susceptibility and adequate body burden, heavy metal exposure from dental amalgam may contribute to imunological aberrations. which could lead to overt autoimunity.

113. MERCURY INDUCES IN VIVO AND IN VITRO SECRETION OF INTERLEUKIN-1 IN MICE. IMMUNOPHARMACOLOGY 1994 NOV;28(3):201-208 ZDOLSEK JM, SODER O, HULTMAN P

Macrophages from SJL and DBA mice incubated with mercuric chloride (HgCl2) in vitro for 24-72 h secreted an increased amount of interleukin 1 (IL-1) to the supernatant compared with control-incubated macrophages, as determined by a sensitive thymocyte proliferation assay. The increase of IL-1 activity showed a highly significant dose-response relationship, being close to that in controls at 10(-8) M, and maximal after incubation with 10(-5)-10(-6) M HgCl2 in both strains. At optimal concentrations of HgCl2 the IL-1 activity started to increase after 6 hrs incubation and reached a maximum after 48 h. Incubation with concentrations of HgCl2 higher than 10(-5) M resulted in a severely reduced IL-1 activity, which correlated with a reduced cell viability. Extracts of HgCl2-incubated macrophages representing cell-bound IL-1 showed no increase in IL-1 activity, irrespective of the concentration or incubation time. Topical application of HgCl2 in a mixture of acetone-olive oil on the external ear of SJL mice induced a dose- and time-dependent increase in IL-1 activity. A maximal increase was seen after application of 1% HgCl2 for 24 h with lower IL-1 activity after 48 and 72 h. Application of 5%, but not 1% or 0. 1%, slightly increased the IL-1 activity in the contralateral ear treated with acetone-olive oil only, as compared with the activity in ears from animals given no mercury treatment, suggesting a systemic effect by application of 5% HgCl2.

114. IMMUNE FACTORS, DENTAL AMALGAM, AND LOW-DOSE EXPOSURE TO MERCURY IN SWEDISH ADOLESCENTS HERRSTROM P, HOLMEN A, KARLSSON A, RAIHLE G, SCHUTZ A, HOGSTEDT ARCHIVES OF ENVIRONMENTAL HEALTH. 49(3):160-164, 1994 MAY-JUN

Abstract Occupational high-dose exposure to metallic mercury can cause immune isturbances in sensitive individuals. Whether low-dose exposure to inorganic mercury from dental Amalgam has this effect in humans is one of the issues related to the concept of oral galvanism and is supported by results of animal studies. This study explored some cellular immune factors (B- and T-lymphocytes, T4, T8, monocytes, neutrophilic, eosinophilic, and basophilic granulocytes, and large unstained cells) and some humoral immune factors (immunoglobulins IgC, IgG1, IgC2, IgC3, IgG4, IgA, IgM, IgE, albumin, alfa-1-antitrypsin, orosomucoid, haptoglobin, and antinuclear antibodies) in 41 healthy 15-y-old schoolchildren. The relationship between these factors and amalgam fillings and mercury concentrations in plasma (P-Hg) were investigated. A low, but significant correlation ($r = 0.40$, $p < .05$) was found between the number of amalgam surfaces and the P-Hg values, which were low for both sexes (median value = 1.8 nmol/l). There was no significant influence of the number of amalgam surfaces or P-Hg on the immune factors tested, except random findings. The girls had significantly higher values of T8, IgG, and IgG1 than the boys.

115. THE BEHAVIOUR OF T-CELL SUBPOPULATIONS IN THE BLOOD OF WORKERS EXPOSED TO MERCURY. MOSZCZYNSKI, P; SLOWINSKI, S. MED LAV. (1994): 85(3), 239-41, MAY-JUN.

ABSTRACT: In 55 men with a history of exposure to mercury vapours, and 36 men without such exposure, the count of T-cells, helper T-cells, suppressor T-cells and NK-cells in peripheral blood was determined using monoclonal antibodies. The concentration of mercury in the urine of the exposed individuals was x = 54, S.D. = 45 micrograms xl-1, and in blood x = 4.7, S.D. = 7.2 micrograms xl- 1.

BIO-PROBE COMMENT:
The evidence that low level exposure to mercury vapour has adverse effects on the immune system continues to mount. Recently published research has attributed this effect to mercury (and silver) derived from dental amalgam (Hultman, P; et al. 1994. See: BPNL, 10(6), Nov 1994). The implications of this research on the health of subjects with amalgam dental fillings is indeed profound

116. CYTOTOXICITY AND ACCUMULATION OF HG, AG, CD, CU, PB AND ZN IN HUMAN PERIPHERAL T AND B LYMPHOCYTES AND MONOCYTES IN VITRO. STEFFENSEN IL MESNA OJ ANDRUCHOW E NAMORK E HYLLAND K ANDERSEN RA GEN PHARMACOL (1994 DEC) 25(8):1621-33

The cytotoxic effects of various heavy metals were assayed by trypan blue exclusion in vitro in human peripheral immune cells separated to high purity. T and B lymphocytes and monocytes were equally sensitive to metals. The individual metals could be ranked in the following decreasing order of cytotoxic potency, Hg approximately Ag > Cd approximately Cu > Pb approximately Zn, based on exposure time and concentration needed to give a particular percentage of dead cells. 2. The cytotoxic effects became irreversible after about 13 hr of metal exposure. 3. Examination by scanning electron microscopy showed that the heavy metals caused serious destruction of the cell membranes. 4. Solubility and uptake of metals into the cells were studied and discussed in relation to the cytotoxic effects. It was concluded that metal binding to cell surfaces or precipitate formation could inhibit ordinary uptake, thereby affecting cytotoxicity. For Pb in monocytes this appeared to lead to uptake of non-toxic complexes, probably by phagocytosis.

117. IMPROVEMENT OF TH1 FUNCTIONS DURING THE REGULATION PHASE OF MERCURY DISEASE IN BROWN NORWAY RATS. CASTEDO M PELLETIER L PASQUIER R DRUET P SCAND J IMMUNOL (1994 FEB) 39(2):144-50

Brown Norway (BN) rats are poor responders to T-cell mitogens and alloantigens when compared to Lewis (LEW) rats. This is dependent partly upon a defect in IL-2 production. The TH2-mediated immune abnormalities observed in BN rats injected with mercuric chloride (HgCl2) are self-limited and it is probable that this regulation phase involves TH1-like cells. This paper reports on a study of the ability of lymph node cells (LNC) from normal BN and LEW rats and from HgCl2-injected BN rats to produce IL-2 and to proliferate when stimulated in vitro by Con A or alloantigens in mixed lymphocyte reaction (MLR), as well as to develop a cytotoxic T lymphocyte (CTL) response to alloantigens. This study will confirm that LNC from BN rats proliferate less than LNC from LEW rats, that the former produce less IL-2 than the latter, and that the proliferative response is restored partially after addition of IL-2. In addition, it is shown (1) that the CTL response is defective in normal BN rats when compared to that of normal LEW rats, and (2) that, after the second week of HgCl2 injections, the proliferative responses to Con A and alloantigens are improved as well as IL-2 production, and a complete

restoration of CTL function is observed. These results show that normal BN rats are deficient in the induction of TH1-like cells and that, from the second week of HgCl2 injections, these TH1 functions improve.

118. EXPOSURE TO MERCURY AND POPULATION HEALTH. I. IMMUNOTOXICITY OF MERCURY MOSZCZYNSKI P MOSZCZYNSKI P MED PR (1995) 46(4):385-93

The authors present large numbers of data on influence of the various mercury compounds on the immune system of humans and laboratory animals. The effect of mercury on the immune system was studied mainly in small rodents intoxicated mostly with HgCl2 or methylmercury. Contrary to a number of these data, analogous observations in humans are rare. Stimulating activity of mercury vapours on the immunological system has been reported in workers at chloralkali plants. So far no data are available concerning influence of the mercury vapours on the resistance of humans to neoplasms and infections.

119. EFFECT OF MERCURY ON THE IMMUNE RESPONSE AND MEAN INTENSITY OF ASCARIS SUUM INFECTION IN GUINEA PIGS. BOROSKOVA Z SOLTYS J BENKOVA M J HELMINTHOL (1995 SEP) 69(3):187-94

The subchronic effect of mercury on selected immunological parameters was studied in guinea pigs with experimental Ascaris suum infection. HgC1(2) given for 28 days reduced significantly T- and B-cell populations in the lymphoid organs and the phagocytic ability of peritoneal macrophages. The subsequent infection of HgC1(2)- intoxicated animals elevated the studied immunological parameters, but in comparison with infected non-intoxicated guinea pigs they remained significantly suppressed. The mercury compound in infection stressed animals caused a slight alteration of the complement CH50 and AH50 activity. The specific circulating antibody level in infected and HgC1(2) treated animals rose a little by day 12 p.i. and then again decreased significantly, compared with untreated guinea pigs. The mean intensity of infection with migrating Ascaris larvae in HgC1(2)-treated animals increased by 15%, compared with controls.

120. ASSESMENT OF MERCURY EXPOSURE AND RISKS FROM DENTAL AMALGAM BY G. MARK RICHARDSON PHD., MEDICAL DEVICES BUREAU, ENVIRONMENTAL HEALTH DIRECTORATE, HEALTH CANADA 1995

Effects caused by allergic hypersensitivity to amalgam or mercury, including possible auto-immune reactions, can not be adequately addressed by any proposed tolerable daily intake. Individuals suspecting any possible allergic or auto-immune reactions should avoid the use of amalgam by selecting suitable alternate materials in consultation with dental care (and possibly health care) professionals.

121. SHORT-TERM CHANGES IN LYMPHOCYTES AFTER PLACEMENT OF SILVER AMALGAM RESTORATIONS IN HEALTHY SUBJECTS. DENT MATER (1995 SEP) 11(5):323-6

OBJECTIVES: The purpose of this study was to evaluate the changes in lymphocyte subpopulations that have led to immune system alterations after amalgam restorations were placed. METHODS: A controlled, quasi-experimental pretest-posttest design was used to investigate the immune effects of silver amalgam restorations in a sample of 60 individuals (30 experimental and 30 control subjects) aged 18 to 21 y. Two blood samples were obtained 15 d apart from each participant. In each experimental subject, two amalgam restorations were placed in posterior teeth immediately after the first blood sample was collected. The changes in lymphocyte subpopulations in the two

groups were compared by multivariate analysis. RESULTS: There was a greater change in T8 lymphocytes in experimental than in control subjects; increases in B, DR, NK, and CD45R lymphocytes were smaller in experimental than in control subjects; the changes in T3 and T4 lymphocytes did not differ significantly between the two groups. SIGNIFICANCE: Despite the statistical significance of some differences between the two groups, the differences are not considered to be clinically relevant for the 2 wk time period after placement.

122. INTERFERON-GAMMA (IFN-GAMMA) AND IL-4 EXPRESSED DURING MERCURY- INDUCED MEMBRANOUS NEPHROPATHY ARE TOXIC FOR CULTURED PODOCYTES COERS W VOS JT VAN DER MEIDE PH VAN DER HORST ML HUITEMA S WEENING JJ CLIN EXP IMMUNOL (1995 NOV) 102(2):297-307

The subepithelial immune deposits of Dorus Zadel Black (DZB) rats with mercury-induced membranous nephropathy consist of autoantibodies directed to laminin P1 and of complement. The animals develop massive proteinuria within 10-14 days which is associated with obliteration of foot processes of glomerular visceral epithelial cells (GVEC), or podocytes. Previous studies indicate that these autoantibodies are probably not the sole mediator of proteinuria and GVEC damage. In this study we investigated whether circulating or macrophage-derived cytokines can contribute to the GVEC changes as detected in vivo. In vivo at the height of the proteinuria, increased intraglomerular IFN- gamma immunoreactivity was found. In diseased rats a five-fold increase in intraglomerular macrophages was found, but we could not detect intraglomerular IFN-alpha, IFN-beta, IL-1 beta or tumour necrosis factor-alpha (TNF-alpha) by using immunohistology. Subsequently, we exposed cultured GVEC to these cytokines to investigate their cytotoxic effects on several physiological and structural parameters. IFN-gamma and IL-4 were the only cytokines that exerted toxic effects, resulting in a rapidly decreased transepithelial resistance of confluent monolayers, which was closely associated with altered immunoreactivity of the tight junction protein ZO-1. IL-4 also affected vimentin and laminin immunoreactivity. IFN-gamma and IL-4 only interfered with monolayer integrity when added to the basolateral side of the GVEC, indicating specific (receptor-mediated) effects. Only IL-4 decreased the viability of the cells, and treated monolayers demonstrated an increased passage of the 44-kD protein horseradish peroxidase. From our experiments we concluded that IFN-gamma subtly affected monolayer integrity at the level of the tight junctions, and that IL-4 additionally induced cell death. We hypothesize that the toxic effects of the cytokines IFN-gamma and IL-4 as seen with cultured podocytes are necessary together with the autoantibodies, for the ultimate induction of proteinuria in mercury nephropathy in the DZB rat.

123. MERCURY HYPERSENSITIVITY FROM AMALGAM: REPORT OF CASE. ULUKAPI I ASDC J DENT CHILD (1995 SEP-OCT) 62(5):363-4

Mercury hypersensitivity is an allergic response mediated by the immune system. allergic reactions to mercury and other constituents of amalgam have been documented, but are very rare. The common symptoms are dermatitis, eczema, urticaria, erythema, edema and itching, occurring primarily on the face, neck, limbs and upper torso. In this paper an interesting case of mercury hypersensitivity is investigated and discussed.

124. MERCURY SUPPRESSION OF A POTASSIUM CURRENT IN HUMAN B LYMPHOCYTES. GALLAGHER JD NOELLE RJ MCCANN FV CELL SIGNAL (1995 JAN) 7(1):31-8

Mercury is a recognized environmental toxin. Several organ systems are targeted by this substance and impairment of immune function is known to result from exposure to mercury. Using the patch clamp technique in the whole cell configuration on resting human B lymphocytes we have identified an outward potassium current and studied the effects of mercury on this current. We present data that demonstrate: (i) the absence of inward currents; (ii) a time and voltage dependent outward current with a threshold of -40 mV and reversal potential near EK+; (iii) blocking of this current by TEA (tetraethylammonium chloride) in a dose dependent manner; (iv) a slow time course for recovery from inactivation of this outwardly rectifying K+ current and, (v) the diminution and final block of this potassium current by mercury. These data supplement the findings from our laboratories that demonstrate inhibitory effects on B cell activation by mercury. We propose that the movement of potassium ions across the B cell membrane, an event presumed to be one of the first signals in the mitogenic process, is a target of mercury toxicity.

125. SYSTEMIC AUTOIMMUNITY DUE TO MERCURY VAPOR EXPOSURE IN GENETICALLY SUSCEPTIBLE MICE: DOSE-RESPONSE STUDIES. WARFVINGE K, HANSSON H, HULTMAN P TOXICOL APPL PHARMACOL 1995 JUN;132(2):299-309

Six groups of genetically mercury-susceptible female SJL/N (H-2s) mice were exposed to mercury vapor at a concentration of 0.3-1.0 mg Hg/m3 air for 0.5-19 hr/day 5 days a week for 10 weeks. The absorbed doses were calculated to be between 75 and 2365 micrograms Hg/week/kg body wt (micrograms Hg/week/kg). The correlation between the dose and the concentration of Hg in kidney, spleen, and thymus was highly significant ($p < 0.0001$; Spearman's rank correlation test). The lowest observed adverse effect level (LOAEL) for serum IgG antinucleolar antibodies (ANoA) was 170 micrograms Hg/week/kg, corresponding to a renal mercury concentration of 4. 0 +/- 0.76 micrograms Hg/g wet wt. The correlation between the absorbed dose and the ANoA titer was highly significant ($p < 0.0001$; Spearman's rank correlation test), and all mice were ANoA-positive at a dose of 480 micrograms Hg/week/kg. High-titer ANoA targeted the nucleolar 34-kDa protein fibrillarin. The LOAEL for B-cell stimulation, measured as an increase in serum IgG2a and IgG1 concentrations, was 360 micrograms Hg/week/kg, but the increase was fivefold higher and also included IgE at a dose of 690 and 2365 micrograms Hg/week/kg. The serum Ig concentrations peaked after 2-4 weeks and then slowly declined but, except for IgE, remained significantly increased during the entire exposure time. Glomerular, mesangial IgG immune complex (IC) deposits, accompanied by systemic vessel wall IC deposits, were first detected at a dose of 480 micrograms Hg/week/kg. The mesangium also showed increased titers of IgM IC deposits and complement factor C3c. The correlation between the absorbed dose, and the individual titer of IgG, IgM, and C3c, was highly significant ($p < 0.0001$; Spearman's rank correlation test). In conclusion, mercury vapor efficiently induced an autoimmune syndrome in genetically susceptible mice, and the LOAEL for the adverse effects varied in the order ANoA < B-cell stimulation < IC deposits. Comparing the body burden of mercury in mice at the LOAEL for autoantibodies with the body burden in populations of occupationally exposed humans suggests that the safety margin may be narrow for genetically susceptible individuals.

126. MURINE MERCURY-INDUCED AUTOIMMUNITY: THE ROLE OF T-HELPER CELLS. HULTMAN P, JOHANSSON U, DAGNAES-HANSEN F J AUTOIMMUN 1995 DEC;8(6):809-823

Genetically mercury-susceptible (H-2s) mice in which the nude (athymic) mutation had been introduced, and euthymic (H-2s) mice treated with anti- CD4 monoclonal antibodies were used to determine the importance of T- helper (CD4+) cells for induction of autoimmunity by mercury, and to study the possibility of using anti-CD4 MAb for treatment of manifest autoimmunity. SJL/N and (A.SW x SJL-nu) F1 x SJL-nu BC (H-2s) mice homozygous for the nude mutation (nu/nu) were treated with 10 mg HgCl2/litre drinking water for 6 weeks. These mice developed neither the antinucleolar antibodies (ANoA) nor the systemic immune-complex (IC) deposits seen in mercury-treated littermates heterozygous for the nude mutation (nu/+). The nu/nu mice showed a significant and substantial reduction of splenocytes with pan-T-(CD3+), T-helper-(CD4+) and T- cytotoxic/suppressor (CD8+) markers, which was accompanied by a severe reduction of the proliferative response to Concanavalin A. Euthymic SJL/N mice given an initial intravenous (i.v.) injection of 100 micrograms anti- CD4 MAb (clone GK 1.5, rat IgG2b), followed by 6 weeks treatment with 100 micrograms anti-CD4 MAb intraperitoneally (i.p.) every third day in combination with 10 mg HgCl2/litre drinking water, did not develop ANoA or systemic IC-deposits. These features were seen in controls i.p. injected with rat IgG2b and given HgCl2 in the drinking water. The anti-CD4 MAb- treated mice showed very few CD4+ splenocytes, but a significant increase of CD8+ cells and severely impaired T-cell function. The possibility of treating longstanding autoimmune conditions with anti-CD4 MAb was examined by giving euthymic SJL mice HgCl2 for 3 months, followed by a mercury-free interval of 3 months and finally 7 weekly injections of 1 mg anti-CD4 MAb. This therapy caused a severe reduction of CD4+ cells, but there was no decline in the ANoA titre. In conclusion, induction of systemic autoimmunity by mercury was strictly dependent on T cells, specifically T- helper (CD4+) cells, and mercury-induced ANoA persisted for a long time after stopping mercury treatment. At this late stage, the autoimmune condition was no longer amenable for anti-CD4 MAb therapy.

127. MERCURY EXPOSURE FROM "SILVER" TOOTH FILLINGS: EMERGING EVIDENCE QUESTIONS A TRADITIONAL DENTAL PARADIGM. LORSCHEIDER, FL; VIMY, ML; SUMMERS, AO. FASEB J. 9:504-508. APR 1995.

ABSTRACT For more than 160 years dentistry has used silver amalgam, which contains approximately 50% Hg metal, as the preferred tooth filling material. During the past decade medical research has demonstrated that this Hg is continuously released as vapour into mouth air, then it is inhaled, absorbed into body tissues, oxidised to ionic Hg, and finally covalently bound to cell proteins. Animal and human experiments demonstrate that the uptake, tissue distribution and excretion of amalgam Hg is significant, and that dental amalgam is the major contribution source to Hg body burden in humans.

Current research on the Pathophysiological effects of amalgam Hg has focused upon the immune system, renal system, oral and intestinal bacteria,reproductive system, and the central nervous system. Research evidence does not support the notion of amalgam safety.

128. FUORTES LJ WEISMANN DN GRAEFF ML BALE JF TANNOUS R PETERS C IMMUNE THROMBOCYTOPENIA AND ELEMENTAL MERCURY POISONING. J TOXICOL CLIN TOXICOL (1995) 33(5):449-55

Three cases of severe mercury toxicity occurring within a family are reported. Two cases of thrombocytopenia occurred in this family and represent the second such report in the literature of an association between elemental mercury toxicity and thrombocytopenia. Three of the children presented with a combination of dermatologic and neurologic manifestations reminiscent of acrodynia or pink disease. Each of the four children in this family were treated with dimercaptosuccinic acid. The hazard of vacuuming spilled mercury and appropriate clean- up procedures are described.

129. AL-BALAGHI S MOLLER E MOLLER G ABEDI-VALUGERDI M MERCURY INDUCES POLYCLONAL B CELL ACTIVATION, AUTOANTIBODY PRODUCTION AND RENAL IMMUNE COMPLEX DEPOSITS IN YOUNG (NZB X NZW)F1 HYBRIDS. EUR J IMMUNOL (1996 JUL) 26(7):1519-26

It is well established that in susceptible mouse strains, chronic treatment with subtoxic doses of mercuric chloride (HgCl2) induces a systemic autoimmune disease, which is characterized by increased serum levels of IgG1 and IgE antibodies, by the production of anti- nucleolar antibodies and by the development of immune complex- mediated glomerulonephritis. Susceptibility to mercury is partly under the control of major histocompatibility complex genes. To study the susceptibility to mercury further, we investigated the in vivo effects of mercury in young autoimmune disease prone (NZB x NZW)F1 (H- 2d/z) mice prior to establishment of spontaneous autoimmune disease. Mercury-susceptible SJL (H-2s) mice and mercury low-responder BALB/c (H-2d) mice were used as positive and negative controls, respectively. In (NZB x NZW)F1 mice, treatment with mercury stimulated an intense antibody formation characterized by increased numbers of splenic IgG1 and IgG3 antibody-producing cells as well as by elevated serum IgE levels. Injection with mercury also induced an increased production of IgG1, IgG2b and IgE antibodies in SJL, but not in BALB/c mice. The mercury-induced IgG1 response in (NZB x NZW)F1 and SJL mice was found to be polyclonal and autoantibodies against double-stranded (ds)DNA, IgG, collagen, cardiolipin, phosphatidylethanolamine as well as antibodies against the hapten trinitrophenol were produced. In addition, SJL, but not (NZB x NZW)F1 or BALB/c mice, produced IgG1 anti-nucleolar antibodies after treatment with mercury. Further studies demonstrated that (NZB x NZW)F1 and SJL mice developed high titers of renal mesangial immune complex deposits containing IgG1 antibodies 3 weeks after injection with mercury. Thus, a mouse strain genetically prone to develop spontaneous autoimmune diseases is highly susceptible to mercury- induced immunopathological alterations.

130. LOWELL JA BURGESS S SHENOY S CURCI JA PETERS M HOWARD TK MERCURY POISONING ASSOCIATED WITH HIGH-DOSE HEPATITIS-B IMMUNE GLOBULIN ADMINISTRATION AFTER LIVER TRANSPLANTATION FOR CHRONIC HEPATITIS B. LIVER TRANSPL SURG (1996 NOV) 2(6):475-8

131. CHRISTENSEN MM HISTOCHEMICAL LOCALIZATION OF AUTOMETALLOGRAPHICALLY DETECTABLE MERCURY IN TISSUES OF THE IMMUNE SYSTEM FROM MICE EXPOSED TO MERCURIC CHLORIDE. HISTOCHEM J (1996 MAR) 28(3):217-25

The distribution of mercury in the spleen, liver, lymph nodes, thymus and bone marrow was studied by autometallography in mice exposed to mercuric chloride intraperitoneally. Application of immunofluorescence histochemistry and an autometallographic silver amplification method was employed to the same tissue section. Mercury was not only detected in macrophages marked by the antibody M1/70 but also in macrophage-like cells, which were either autofluorescent or devoid of fluorescent signals. These two cell types were identified as macrophages at the electron microscopical level. Autometallographically stained macrophages were observed in the spleen, lymph nodes, thymus and in Kupffer cells of the liver. Furthermore, mercury was observed in endothelial cells. No obvious pathological disturbances were observed at light and electron microscopical level. At the subcellular level mercury was localized in lysosomes of macrophages and endothelial cells.

132. BARREGARD L ENESTROM S LJUNGHUSEN O WIESLANDER J HULTMAN P A STUDY OF AUTOANTIBODIES AND CIRCULATING IMMUNE COMPLEXES IN MERCURY- EXPOSED CHLORALKALI WORKERS. INT ARCH OCCUP ENVIRON HEALTH (1997) 70(2):101-6

Inorganic mercury may cause immunologically mediated disease: e.g., glomerulonephritis, acrodynia, and contact allergy. Animal models have demonstrated the importance of genetic factors in determining susceptibility and resistance to autoimmunity, as well as the specific manifestation of the autoimmune response. Findings in groups of workers with occupational exposure to inorganic mercury have been inconsistent. OBJECTIVE: To investigate whether an immune response, caused by exposure to inorganic mercury (Hg), could be shown in occupationally exposed workers. METHODS: Immunoglobulin G (IgG), antinuclear autoantibodies, antibodies against thyroid, stomach or kidney antigens using indirect immunofluorescence, antibodies against glomerular basement membrane using ELISA, and circulating immune complexes in serum, and albumin in urine, were examined in Hg-exposed workers and controls. The two groups, 41 male chloralkali workers exposed to Hg vapour (mean exposure time 9 years) and 41 unexposed controls were age-matched and recruited from the same company. Hg concentrations in whole blood (B-Hg), plasma (P-Hg), and urine (U-Hg) were determined using cold vapor atomic spectrometry. DESIGN: Cross- sectional study. RESULTS: The mean B-Hg, P-Hg and U-Hg levels were 46 nmol/l, 37 nmol/l, and 27 micrograms/g creatinine in the exposed group, and 17 nmol/l, 6.9 nmol/l, and 3.4 micrograms/g creatinine in the referents. No statistically significant differences were found regarding IgG levels, urinary albumin excretion, prevalence of abnormal titers of autoantibodies or circulating immune complexes. There were no statistically significant associations between autoantibodies or immune complexes on the one hand and mercury exposure indices on the other. CONCLUSION: The results indicate that, if and when lasting autoimmune response occurs at the mercury exposure levels of the present study, it is uncommon. A small fraction of humans may, however, be susceptible to the development of autoimmunity,

and there is also a possible "healthy worker" selection. Thus cross-sectional studies of moderate numbers of active workers will have low power to demonstrate autoimmune effects.

133. MOSZCZYNSKI P MERCURY COMPOUNDS AND THE IMMUNE SYSTEM: A REVIEW. INT J OCCUP MED ENVIRON HEALTH (1997) 10(3):247-58

This article reviews the literature data concerning the immunologic monitoring of animals and cell cultures exposed to mercury compounds. Mercury is present in nature as metallic mercury, mono- and bivalent inorganic compounds, and organic alkyl, aryl and alloxy-alkyl compounds. Methylmercury is most important in terms of environmental exposure while metallic mercury is the most common form to which workers are exposed. The database on immune function disturbances in human induced by mercury compounds is limited. Immunotoxicity assessment in animals, mainly in rodents, with subsequent extrapolation to man, is the basis of human risk assessment. The strength of in vitro immunotoxicity testing lies in studies aimed at unravelling mechanisms of immunotoxicity. These experimental investigations show clearly that mercury compounds can have immunomodulating activity. Mercuric chloride and methylmercury inhibit most of animal and human lymphocyte functions including proliferation, expression of cell activation markers on cell surface and cytokine production. These cells exhibit a greater sensitivity to the immunotoxic effects of methylmercury than to mercuric chloride. Repeated administration of mercuric chloride to rats, mice and rabbits can induce autoimmune response and a membranous nephropathy. In contrast, Lewis rats injected with mercuric chloride do not develop autoimmunity but exhibit immunosuppression. The immunosuppressive effects associated with exposure to chemical substances are often accompanied by increased susceptibility to challenge with infectious agents or tumour cells. Only few reports are available on animal studies of increased mortality connected with exposure to mercury compounds and challenge with infectious agents. It is difficult to establish a relationship between the observed immunomodulatory properties of mercury compounds and their possible carcinogenicity. In fact, the epidemiological studies performed so far failed to bring any conclusive evidence of carcinogenicity of mercury in animal experiments. The induction of renal tumours in male rodents by methylmercury was observed only.

134. NEUROIMMUNOLOGICAL EFFECTS OF EXPOSURE TO METHYLMERCURY FORMS IN THE SPRAGUE DAWLEY RATS: ACTIVATION OF THE HYPOTHALAMIC - PITUITARY - ADRENAL AXIS AND LYMPHOCYTE RESPONSIVENESS. ORTEGA, HG; LOPEZ, M; TAKAKI, A; HUANG, QH ARIMURA, A, SALVAGGIO, JE. TOXICOL IND HEALTH, 13(1):57-66, 1997.

ABSTRACT: The effects of different methyl mercury (MeHg) forms on the immune system and the hypothalamic pituitary adrenal (HPA) axis were assessed. The lymphocyte response to Concanavalin A (Con A) stimulation, blood levels of interleukin-6 (IL-6), adrenocorticotrophin hormone (ACTH), and corticosterone in the presence of different MeHg compounds was measured. Rats were exposed to methyl mercury

sulfide [(MeHg)2S] and methyl mercury chloride (MeHgCI) at concentrations of 5 and 500 micrograms per lifer in the drinking water for 8 or 16 weeks.

Short term exposure (8 weeks) at both, low and high doses of (MeHg)2S significantly enhanced lymphocyte responsiveness. MeHgCI only induced increased lymphocyte responsiveness at the low dose exposure. Circulating levels of IL-6 after short term exposure were increased in the MeHgCI exposed group. The HPA axis activation was demonstrated by increased levels of ACTH and corticosterone levels. This response was predominant in low dose exposed animals. Long term (16 weeks) exposure resulted in a reduction in lymphocyte prolife ration after both low and high dose MeHgCI exposures. The (MeHg)2S exposure resulted m a 3 fold increase in the proliferative response. Levels of ACTH were elevated 3 fold in the (MeHg) 2S exposed group and no increase of corticosterone was observed in the high dose exposed group at 8 weeks, no effect of (MeHg)2S was observed at 16 weeks. The MeHgCI exposed group showed an increase in ACTH and corticosterone levels at 8 weeks; this response was not observed at 16 weeks.

These data indicate that exposure to MeHg compounds enhances T cell proliferation in most of the cases, in a dose and time dependent fashion. Release of IL-6 also depends on the length of exposure. Early increases in circulating ACTH at 8 weeks also suggest activation of the HPA axis. This may contribute to the production of IL-6 and surveillance of regulatory homeostatic responses against environmental agents that mimic stress-like responses.

135. THIOL COMPOUNDS INHIBIT MERCURY INDUCED IMMUNOLOGICAL AND IMRNUNOPATHOLOGICAL ALTERATIONS IN SUSCEPTIBLE MICE. HU, H; MOLLER, G; ABEDI-BALUGERDI, M. CLIN EXP IMMUNOL, 107(1):68-75, JAN 1997.

ABSTRACT: In vitro mercury induces a high proliferative response in splenic lymphocytes and in vivo it induces a systemic autoimmune disease in susceptible mouse strains. This disease is characterized by increased serum levels of IgE and IgG1 antibodies, by the production of anti- nucleolar antibodies and by the formation of renal immune complex deposits.

We have previously found that the presence of 2-mercaptoethanol (2-ME) inhibited mercury induced cell proliferation in vitro. In this study, we tested the effects of four other thiol compounds, namely dithiothreitol (DTT), L-cysteine, meso-2,3dimercaptosuccinic acid (meso-DMSA) and 2,3- dimercapto-1-propanesulfonic acid, Na salt (DMPS) on mercury induced immunological changes both in vitro and In viva.

We found that in vitro, the addition of all thiol compounds abrogated mercury induced cell aggregation and proliferation. In viva, injection of mesoDMSA and/or DMPS (s.c. or i.p.) Immediately following exposure to mercury markedly decreased IgGl synthesis in spleen cells and serum IgE levels in mercury susceptible SJL mice. Treatment with DMPS also prevented mercury induced IgGl antinucleolar antibody synthesis and the development of mesangial IgGl immune complex deposits in SJL mice.

136. MERCURY COMPOUNDS AND THE IMMUNE SYSTEM: A REVIEW. MOSZCZYSKI, P. INT J OCCUP MED ENVIRON HEALTH, 10(3):247-58, 1997.

ABSTRACT: This article reviews the literature data concerning the immunologic monitoring of animals and cell cultures exposed to mercury compounds. Mercury is present in nature as metallic mercury, mono- and bivalent inorganic compounds and organic alkyl, aryl and alloxy-alkyl compounds. Methyl mercury is most important in terms of environmental exposure while metallic mercury is the most common form to which workers are exposed.

The database on immune function disturbances in humans induced by mercury compounds is limited. Immunotoxicity assessment in animals, mainly in rodents, with

subsequent extrapolation to man, is the basis of human risk assessment. The strength of in vitro immunotoxicity testing lies in studies aimed at unraveling mechanisms of immunotoxicity. These experimental investigations show clearly that mercury compounds can have immunomodulating activity. Mercuric chloride and methyl mercury inhibit most of animal and human lymphocyte functions including proliferation, expression of cell activation markers on cell surface and cytokine production. These cells exhibit a greater sensitivity to the immunotoxic effects of methyl mercury than to mercuric chloride. Repeated administration of mercuric chloride to rats, mice and rabbits can in duce autoimmune response and a membranous neprhopathy. In contrast, Lewis rats injected with mercuric chloride do not develop autoimmunity but exhibit immunosuppression. The immunosuppressive effects associated with exposure to chemical substances are often accompanied by increased susceptibility to challenge with infections agents or tumor cells.

Only few reports are available on animal studies of increased mortality connected with exposure to mercury compounds and challenge with infectious agents. It is difficult to establish a relationship between the observed immunomodulatory properties of mercury compounds and their possible carcinogenicity. In fact, the epidemiological studies performed so far failed to bring any conclusive evidence of carcinogenicity of mercury in animal experiments.

137. ORAL, PERIORAL AND SYSTEMIC PATHOSIS IN HGCL2-INDUCED AUTOIMMUNITY IN THE BN RAT. WARFVINGE G, PESZKOWSKI MJ, HULTMAN P, LARSSON A EUR J ORAL SCI 1997 APR;105(2):153-161

Male BN rats were repeatedly skin-injected with HgCl2 solution and sacrificed after 6, 9, 14, 21, 28 or 24 days. Mononuclear cell infiltrates were observed in the oral mucosa and in lacrimal, salivary and thyroid glands from 6-9 days onwards, with a peak at 14-21 days. Immunohistochemistry identified these cells as predominantly T cells with some NK cells but very few B cells. Reversible parenchymal changes were observed but there was no obvious persistent tissue destruction. Serum titers of IgE, IgG1, anti-laminin and anti-DNP, but not IgG2a antibodies, were raised and peaked at 14-21 days. However, there was no correlation, within animals, between these titers and the extent of mononuclear cell infiltration. Mercury was histochemically detected within dendritic cells/macrophages in the connective tissue stroma of the glands and in the oral mucosa, but no correlation was found between the distribution of mercury and the degree of inflammation. We conclude that the accumulation of mononuclear cells in oral and perioral tissues of HgCl2-treated BN rats does not represent a local immune response to tissue-retained Hg. Instead, we propose that the extravasation represents an epiphenomenon that is not necessarily deleterious to the infiltrated organ.

138. BAUER R MULLER A RICHTER M SCHNEIDER K FREY J ENGELHARDT W INFLUENCE OF HEAVY METAL IONS ON ANTIBODIES AND IMMUNE COMPLEXES INVESTIGATED BY DYNAMIC LIGHT SCATTERING AND ENZYME-LINKED IMMUNOSORBENT ASSAY. BIOCHIM BIOPHYS ACTA (1997 FEB 11) 1334(1):98-108

The effect of Cd2+, Pb2+, Hg2+ and Cu2+ on the aggregation behaviour of monoclonal rat-IgG1-anti-mouse antibodies (kappa-light chain specific) and their antibody-antigen complexes with monoclonal mouse- IgG1 is reported. Investigations were done using the dynamic light scattering method. Cd2+ ions affected the hydrodynamic properties of the antibodies and the immune complex formation very little. More than 4 Cu2+ ions per antibody molecule led to large insoluble aggregates. Pb2+ ions also interacted

with antibodies and immune complexes. Instead of "monomeric' antibodies (Ab) or immune complexes (Ab1Ag1), large soluble aggregates were detectable in the solution. Hg2+ ions induced complex formation with 3-4 antibodies per aggregate. Possible kinds of interaction are discussed. Additionally, we tested the antigen binding activity of metal-treated antibodies in ELISA-tests. The Sandwich ELISA technique was used to investigate the serological activity of the metal-treated antibodies, i.e., the reaction with the specific antigen. For these experiments we used the same monoclonal antibodies, mouse-IgG1 and rat-IgG1-anti-mouse. The influence of the above mentioned heavy metal ions was investigated up to a 10-fold molar excess over the antibody concentration. Even at these "unphysiological' high metal ion concentrations an inhibition of the antibody-antigen binding activity was not detectable.

139. MERCURY-INDUCED RENAL IMMUNE COMPLEX DEPOSITS IN YOUNG (NZB X NZW)F1 MICE: CHARACTERIZATION OF ANTIBODIES/AUTOANTIBODIES. ABEDI-VALUGERDI M HU H MOLLER G CLIN EXP IMMUNOL (1997 OCT) 110(1):86-91

It is well demonstrated that mercury induces a systemic autoimmune disease in susceptible mouse strains. One of the major characteristics of mercury-induced autoimmune disease in mice is the development of renal immune complex deposits. We have previously shown that continual injection of mercury into young autoimmune prone (NZB x NZW)F1 mice induced an increase in antibody/autoantibody production as well as development of early renal immune complex deposits. In the present study, we characterized the isotype, the specificity and the possible pathogenicity of deposited immunoglobulins in the kidneys of mercury-injected (NZB x NZW)F1 hybrids. We found that young (NZB x NZW)F1 mice injected with mercuric chloride (HgCl2) for 6 weeks developed intense antibody formation of all immunoglobulin isotypes (except for IgG2b) as well as high levels of granular deposits of IgM, IgG1, IgG2a and IgG3 antibodies in the renal mesangium. Increased levels of the same antibody isotypes were also found in the kidney eluate of mercury- but not saline-injected mice. The dominant antibody in the kidney eluate of mercury-injected mice was of IgG1 isotype and found to be directed against double-stranded DNA, collagen, cardiolipin, phosphatidylethanolamine, and the hapten trinitrophenol, but not against nucleolar antigens. Further studies demonstrated that mercury- induced renal immune complex deposits in young (NZB x NZW)F1 mice did not lead to a severe kidney injury. Thus, in response to mercury, young (NZB x NZW)F1 mice develop renal immunoglobulin deposits with an isotype and specificity pattern correlating with that seen in the spleen and in the serum.

140. MURINE SILVER-INDUCED AUTOIMMUNITY: SILVER SHARES INDUCTION OF ANTINUCLEOLAR ANTIBODIES WITH MERCURY, BUT CAUSES LESS ACTIVATION OF THE IMMUNE SYSTEM. JOHANSSON U HANSSON-GEORGIADIS H HULTMAN P INT ARCH ALLERGY IMMUNOL (1997 AUG) 113(4):432-43

BACKGROUND: Mercury and silver induce antinucleolar autoantibodies (ANoA) targeting the 34-kDa nucleolar protein fibrillarin in susceptible mouse strains. Mercury has the ability to cause a general activation of the immune system, but antigen-specific mechanisms following direct or indirect interaction between mercury and fibrillarin are now believed to play a crucial role in the autoimmune pathogenesis. Our previous studies showed that silver neither induced the systemic immune complex deposits nor the increase of serum immunoglobulins seen after mercury treatment. The main objective of this study was to examine the relation between activation of the immune system and the induction of ANoA. METHODS: During 4 weeks of subcutaneous silver

nitrate injections into mice of the susceptible A.SW and SJL strains and the resistant A.TL strain, the number of T and B cells as well as the expression of cell surface activation and proliferation markers were monitored by flow cytometry. The number of cytoplasmic Ig+ splenocytes was determined by direct immunofluorescence technique on slides, and serum Ig levels as well as anti-ssDNA anti anti-DNP antibodies were determined by ELISA. Serum ANoA were monitored by the indirect immunofluorescence technique. RESULTS: Silver caused in the susceptible strains a weaker and later activation and proliferation of T and B cells than mercury, and no significant polyclonal B cell activation. In contrast, the ANoA titer was not different from that seen in mercury-treated mice of the same strains. Silver-treated mice of the A.TL strain showed neither activation of the immune system nor ANoA. CONCLUSIONS: Despite being as effective as mercury inducing ANoA, silver caused only a slight activation of the immune system. This demonstrates that the massive activation of the immune system in mercury treatment is not necessary for the induction of ANoA, and indicates that (auto)antigen-specific mechanisms are likely to play a key role in mercury- and silver-induced murine autoimmunity.

141. WILD LG ORTEGA HG LOPEZ M SALVAGGIO JE IMMUNE SYSTEM ALTERATION IN THE RAT AFTER INDIRECT EXPOSURE TO METHYL MERCURY CHLORIDE OR METHYL MERCURY SULFIDE. ENVIRON RES (1997) 74(1):34-42

Methyl mercury is a well-recognized health hazard. It is an environmental contaminant that accumulates in the food chain. The primary source of mercury exposure for humans is through the consumption of contaminated fish. We studied the effects of indirect methyl mercury exposure on the immune system of Sprague-Dawley rats. The effects of different forms of methyl mercury on immune system development were studied in Sprague-Dawley rats at 6 and 12 weeks of age. Rats were indirectly exposed to mercury during gestation and during nursing by exposing pregnant rats to either 5 or 500 micrograms/liter of methyl mercury chloride (CH3HgCl) or 5 micrograms/liter of methyl mercury sulfide [(CH3Hg)2S] in their drinking water. Total body, splenic, and thymic weights were measured, and NK cell cytolytic activity and lymphoproliferative response to T and B cell mitogens were evaluated in the offspring. At 6 weeks of age, total body and splenic weights were significantly increased in both high- and low-dose methyl mercury chloride-exposed groups. Rats exposed to methyl mercury sulfide had a significant increase in thymic weight at 6 weeks of age. At 12 weeks, the total body and organ weights were not different from controls. The lymphocyte proliferative response of splenocytes to PWM was enhanced at 6 weeks in both CH3HgCl exposed groups and not affected in the (CH3Hg)2S exposed group. NK cell activity was not affected in either group at 6 weeks of age. At age 12 weeks, NK cell activity was statistically significantly decreased by 56.6% in both CH3HgCl- exposed groups and not affected in the (CH3Hg)2S-exposed rats. The lymphocyte proliferative response of splenocytes to the B cell mitogen pokeweed remained increased in the CH3HgCl groups. Indirect exposure of rats (during gestation and nursing) to different forms of methyl mercury reveals that chloride forms have prolonged predominantly enhancing effects on lymphoproliferative response of splenocytes, followed by significant depression of NK cell activity.

142. Inorganic mercury modifies Ca2+ signals, triggers apoptosis, and potentiates NMDA toxicit in cerebral granule neurons. Cell Death and Differentiation Rossi AD,Viviani B, Vahter M. 1997; 4(4):317-24.

143. Roitman MI Karamova LM Karaseva IuB Fukalova LA Khavkin IuA Importance of variation criteria in statistical evaluation of the immune status of work crews. Med Tr Prom Ekol (1998)(1):30-

Variation criteria--variation coefficient, Fisher criterion (F-value) and suggested by the authors index of homeostasis--enable to evaluate completely the state of occupational crews and reveal their compensated disadaptation. Administration of adaptogens (such as oxymethacil) is expedient for correction of premorbid conditions in occupational crews. Increased aboriginality and random selection during occupational activities considerably better adaptational characteristics of the occupational crews.

144. MELISA: A New Technology for Diagnosing and Monitoring of Metal Sensitivity, V.Stejskal, Proceedings: 33rd Annual Meeting of American Acadamy of Environmental Medicine, Nov. 1998, Baltimore, Maryland.

145. Activation of the Immune System and Systemic Immune-Complex Deposits in Brown Norway Rats With Dental Amalgam Restorations. Hultman, P; Lindh, U; Horsted-Bindslev, P. J Dent Research, 77(6):1415-25, Jun 1998.

ABSTRACT: Dental amalgam restorations are a significant source of mercury exposure in the human population, but their potential to cause systemic health effects is highly disputed. We examined effects on the immune system by giving genetically mercury susceptible Brown Norway (BN) rats and mercury resistant Lewis (LE) rats silver amalgam restorations in 4 molars of the upper jaw, causing a body burden similar to that described in human amalgam bearers (from 250 to 375 mg amalgam/kg body weight).

BN rats with amalgam restorations, compared with control rats given composite resinous restorations, developed a rapid activation of the immune system, with a maximum 12-fold increase of the plasma IgE concentration after 3 wks ($p < 0.001$; Mann-Whitney's test). LE rats receiving amalgam restorations showed no significant increase of plasma IgE ($p > 0.05$). After 12 wks, BN rats with amalgam restorations showed significantly increased ($p < 0.05$) titers of immune complex (IC) deposits in the renal glomeruli and in the vessel walls of internal organs. These rats also showed a significant ($p < 0.05$), from six- to 130-fold, increase in tissue mercury concentration in the concentration order kidney > spleen > cerebrum occipital lobe > cerebellum > liver > thymus, and the tissue silver concentration was significantly ($p < 0.05$) increased from three- to 11-fold. Amalgam implanted BN rats showed a significant (($p < 0.05$) increase in copper concentration in the kidney and spleen, and in kidney selenium concentration.

We conclude that dental amalgam restorations release substantial amounts of their elements, which accumulate in the organs and which, in genetically susceptible rats, give rise to activation of the immune system and systemic IC deposits.

146. THE EFFECT OF TOXICOKINETICS ON MURINE MERCURY-INDUCED AUTOIMMUNITY. HULTMAN P, NIELSEN JB ENVIRON RES 1998 MAY;77(2):141-148

Mercury induces autoantibodies to the nucleolar protein fibrillarin (ANoA) in genetically susceptible (H-2AS) mouse strains. This study examines the importance of mercury toxicokinetics for the induction and strength (titer) of these autoantibodies. Female mice of the inbred strains A.SW and B10.S (H-2AS on the A and C57BL/10 genetic background, respectively) and A.TL and B10.TL (H-2Ak on the A and C57BL/10 background) were treated with 203HgCl2 in a dose of 1, 5, or 16 mg Hg/L drinking water for 56-70 days. Whole-body retention of 203Hg was monitored throughout the experimental period. Mercury accumulation in kidney, liver, heart, spleen, and brain was determined at end of the experiment when blood samples were also obtained for determination of ANoA. The drinking water consumption showed a limited variation between the strains and the dose groups. Therefore, intake of mercury did not vary much between the strains at a given dose level. The whole-body retention of mercury reached steady state after 4-5 weeks. In general, the B10.S and B10.TL strains showed a lower whole-body retention and deposition of mercury in the kidney and the liver, compared with the A. SW and A.TL strains given the same dose of mercury. The B10.S strain showed a threshold for induction of ANoA at 5 mg Hg/L, whereas ANoA were still seen in A.SW mice given 1 mg Hg/L. Taken together, this is compatible with a less efficient elimination of mercury in the A.SW and A. TL strains, which was also supported by the higher ratio between whole- body retention and intake of mercury in these strains. These findings indicate that genes residing outside the H-2 (MHC) complex play an important role for regulating mercury toxicokinetics, the A genes conferring higher accumulation of mercury in the body than the B10 genes. In mice congenic with regard to the susceptible H-2AS haplotype, a highly significant correlation ($P<0.01$) existed between on the one hand the whole- body retention and organ accumulation of mercury and on the other hand the titer of ANoA. We conclude that mercury toxicokinetics differs significantly among inbred mouse strains. The differences in toxicokinetics are regulated by non-H-2 genes and correlate with the autoimmune response in the genetically susceptible strains: quantitatively as the titer of the ANoA and qualitatively as different threshold doses for induction of ANoA by mercury.

147. LOW-LEVEL METHYLMERCURY EXPOSURE CAUSES HUMAN T-CELLS TO UNDERGO APOPTOSIS: EVIDENCE OF MITOCHONDRIAL DYSFUNCTION. SHENKER BJ, GUO TL, SHAPIRO IM ENVIRON RES 1998 MAY;77(2):149-159

There is growing evidence that heavy metals, in general, and mercurial compounds, in particular, are immunotoxic to the human immune system. The major focus of our study is to demonstrate that methylmercuric chloride (MeHgCl) kills human lymphocytes by inducing apoptosis. T-cells exposed to 0.6-5 microM MeHgCl for 24 h were analyzed by flow cytometry. Methylmercury-treated cells exhibited increased Hoechst 33258 fluorescence while maintaining their ability to exclude the vital stain 7-aminoactinomycin. Furthermore, T-cells exposed to methylmercury exhibited changes in light scatter patterns that included decreased forward light scatter and increased side light scatter. The light scatter and fluorescent changes were consistent with morphological alterations displayed by cells during apoptosis. Cell death was further evaluated by assessing annexin V binding to the plasma membrane. Methylmercury-treated cells exhibited increased annexin V binding indicative of phosphatidylserine translocation to the outer leaflet of the plasma membrane. Using the fluorescent probe DiOC6(3), we noted that methylmercury exposure resulted in a decrease in

mitochondrial transmembrane potential (Psim). Since a low Psim is associated with altered mitochondrial function, we also determined if exposure to methylmercury potentiated reactive oxygen species (ROS) generation. We noted that treated cells generated ROS, as evidenced by oxidation of hydroethidine and the generation of the fluorescent product, ethidium. Finally, we evaluated the effect of methylmercury on T-cell GSH content utilizing the fluorescent probe monochlorobimane; in the presence of MeHgCl, there is a marked loss in reduced cell thiols. The results of the study indicate that a key event in the induction of T-cell apoptosis by mercuric compounds is depletion in the thiol reserve which predisposes cells to ROS damage and at the same time activates death signaling pathways. Copyright 1998 Academic Press.

148. EFFECTS OF MERCURIC CHLORIDE AND SODIUM SELENITE ON SOME IMMUNE RESPONSES OF BLUE GOURAMI, TRICHOGASTER TRICHOPTERUS (PALLUS). LOW KW, SIN YM SCI TOTAL ENVIRON 1998 JUN 18;214:153-164

The immunotoxicological effects of mercuric chloride and sodium selenite on blue gourami were studied. Some immune responses ranging from non- specific to specific were investigated. These include tissue lysozyme activity, kidney lymphocyte proliferation and plasma agglutinating antibody titre against bacteria. After 2 weeks of chronic exposure, 0.09 mg/l of Hg2+ alone induced a significant increase of kidney lysozyme activity of 4196.3 +/- 1171.0 U/g, but it decreased to 1577.4 +/- 902.4 U/g when exposed simultaneously to equiconcentration of selenium. Plasma lysozyme activity was also increased by co-administration of Hg2+ and SeO3(2-). The level of plasma agglutinating antibody against Aeromonas hydrophila L37 was lowered in the chemical-treated fish. This indicates that the fish immunity was impaired by action of mercury and selenium. However, the in vitro lymphocyte proliferation test shows that mercury concentration lower than 0.045 mg/l Hg2+ enhanced the mitotic rate of kidney lymphocytes by approximately 30%. A high concentration of mercury caused irreversible damaging effects on con A-induced lymphoblastogenesis. In contrast, the inhibitory effect of low concentrations of mercury could be removed by washing. On the other hand, selenium showed a suppressive effect on the lymphocyte proliferation even at 0.5 mg/l.

149. ACTIVATION OF THE IMMUNE SYSTEM AND SYSTEMIC IMMUNE-COMPLEX DEPOSITS IN BROWN NORWAY RATS WITH DENTAL AMALGAM RESTORATIONS. HULTMAN P, LINDH U, HORSTED-BINDSLEV P J DENT RES 1998 JUN;77(6):1415-1425

Dental amalgam restorations are a significant source of mercury exposure in the human population, but their potential to cause systemic health effects is highly disputed. We examined effects on the immune system by giving genetically mercury-susceptible Brown Norway (BN) rats and mercury- resistant Lewis (LE) rats silver amalgam restorations in 4 molars of the upper jaw, causing a body burden similar to that described in human amalgam-bearers (from 250 to 375 mg amalgam/kg body weight). BN rats with amalgam restorations, compared with control rats given composite resinous restorations, developed a rapid activation of the immune system, with a maximum 12-fold increase of the plasma IgE concentration after 3 wks ($p < 0.001$; Mann-Whitney's test). LE rats receiving amalgam restorations showed no significant increase of plasma IgE ($p > 0.05$). After 12 wks, BN rats with amalgam restorations showed significantly increased ($p < 0.05$) titers of immune-complex (IC) deposits in the renal glomeruli and in the vessel walls of internal organs. These rats also showed a

significant ($p < 0.05$), from six- to 130-fold, increase in tissue mercury concentration in the concentration order kidney > spleen > cerebrum occipital lobe > cerebellum > liver > thymus, and the tissue silver concentration was significantly ($p < 0.05$) increased from three- to 11-fold. Amalgam-implanted BN rats showed a significant ($p < 0.05$) increase in copper concentration in the kidney and spleen, and in kidney selenium concentration. We conclude that dental amalgam restorations release substantial amounts of their elements, which accumulate in the organs and which, in genetically susceptible rats, give rise to activation of the immune system and systemic IC deposits.

150. From the Press Conference of the Swedish Council for Planning and Coordinating Research Stockholm 19 February 1998.

"Amalgam can cause brain damage in children"
-Move over amalgam - at last!

Mercury from amalgam may damage the brain, kidneys and the immune system of a great number of people. The effects in foetus and children are of most concern. Those are the conclusions of a report soon to be handed to the Government."There is no conflict any more", says Gunnar Goude from the board of the Swedish Council for Planning and Coordinating Research (FRN), after reviewing the comprehensive documentation from the four seminars. " There is total agreement among the Board members that it is time to move forward and leave amalgam behind". The Board will, in their coming report to the Government, recommend the discontinued use of amalgam as a dental material.

151. Swedish Government Report On Dental Amalgam and Mercury Title: Dental Materials and Health Author: Maths Berlin

Studies of the effects of mercury on the immune system in rodents have enhanced knowledge of the mechanisms whereby mercury affects the immune system. Clinical studies of occupationally exposed employees have objectively confirmed subclinical influence of mercury on the immune system at low levels of mercury exposure.

152. Evidence for heterogeneous TCR V beta repertoire expression in mercury-induced immune disorders in rats. Fillion J Baccala R Pannetier C Kuhn J Druet P Bellon B Int Immunol (1997 Feb) 9(2):263-71

Administration of subtoxic doses of $HgCl_2$ affects differentially the immune system depending on the strain of rats tested. Susceptible Brown-Norway (BN) rats exhibit a CD4+ T cell-dependent polyclonal activation of B cells; in contrast, Lewis (LEW) rats are resistant and develop an immunosuppression mediated by CD8+ T cells recruited by CD4+ T cells. The mechanisms by which mercury induces immune disorders are poorly understood. We were interested in analyzing the diversity and mercury-mediated changes of the TCR Vbeta repertoire in the BN and LEW strains of rats at different times of $HgCl_2$ exposure. Our results obtained after analysis of lymph node T cells by RNase protection assay, flow cytometry or immunoscope assay (i) were not consistent with a superantigen-like stimulus since we observed neither a V beta-selective expansion nor deletion that would have been expected and (ii) showed that in BN rats, as well as in LEW rats, an increase in the number of T cells was associated with the heterogeneous TCR V beta repertoire, thus supporting a polyclonal T cell activation. However, in BN rats

the total number of T cells increased very rapidly, whereas in LEW rats only CD8+ T cells accumulated.

153. ACUTE EXPOSURE TO MERCURY FROM AMALGAM: NO SHORT-TIME EFFECT ON THE PERIPHERAL BLOOD LYMPHOCYTES IN HEALTHY INDIVIDUALS. LOFTENIUS A, SANDBORGH-ENGLUND G, EKSTRAND J J TOXICOL ENVIRON HEALTH (1998 AUG 7) 54(7):547-60

Mercury, released from dental amalgam, has been considered to adversely affect the human immune system. This study has been performed in order to evaluate if an acute low-dose mercury exposure, achieved by total amalgam removal in 10 healthy individuals, would affect the immunocompetent cells in human blood when the mercury level in blood and plasma was increasing. Induction of lymphocyte proliferation, measured as spontaneous de novo DNA synthesis, and total T cells, CD4+ T cells, CD8+ T cells, and B cells, was studied prior to and 7, 31, and 48 h after amalgam removal. In addition, the levels of interleukin-6 (IL-6) and C-reactive protein (CRP) in serum/plasma were measured. Despite a significant increase of the plasma mercury levels within 24 h after intervention, no significant influence on the peripheral blood lymphocytes could be detected during the first 48 h. The serum IL-6 levels increased significantly within 48 h after intervention, but were still low and within normal range. No influence on the CRP levels up to 7 d after amalgam removal was detected.

154. THE PROTOTYPIC TH2 AUTOIMMUNITY INDUCED BY MERCURY IS DEPENDENT ON IFN-GAMMA AND NOT TH1/TH2 IMBALANCE. KONO DH, BALOMENOS D, PEARSON DL, PARK MS, HILDEBRANDT B, HULTMAN P, POLLARD KM J IMMUNOL (1998 JUL 1) 161(1):234-40

Imbalances of Th1- and Th2-type responses have been postulated to be a predisposing factor for both humoral and cellular mediated autoimmune diseases. To further define their roles in systemic autoimmunity, IL-4 and IFN-gamma gene knockout mice were studied for susceptibility to the prototypic Th2-mediated mercury-induced autoimmunity. A predominant Th2- type response following HgCl2 treatment of wild-type B10.S mice was confirmed by the findings of a significant increase in splenic IL-4 and hypergammaglobulinemia primarily of the IgG1 isotype, without an increase in IFN-gamma levels. Paradoxically, IL-4-deficient mice developed the characteristic anti-nucleolar autoantibodies and tissue deposition of immune complexes, while IFN-gamma-deficient mice had very low autoantibody levels and essentially normal immunohistology. Studies to define defects in Ab responses of IFN-gamma-deficient mice, using the T-dependent Ag (4-hydroxy-3-nitrophenyl)acetyl, revealed an attenuated IgG response to low and to a lesser extent high doses of (4-hydroxy-3-nitrophenyl)acetyl-hemocyanin, but maintenance of affinity maturation. These results indicate that Th1/Th2 imbalance does not directly play a role in susceptibility to mercury-induced autoimmunity, and suggest that the dependence on Th1-type responses in certain autoimmune diseases is due to the requirement for IFN- gamma for Ab production to weakly antigenic self molecules.

155. LOW LEVELS OF IONIC MERCURY MODULATE PROTEIN TYROSINE PHOSPHORYLATION IN LYMPHOCYTES. ROSENSPIRE AJ, BODEPUDI S, MATHEWS M, MCCABE MJ JR INT J IMMUNOPHARMACOL (1998 DEC DEC) 20(12):697-707

The ability of ionic mercury to induce protein tyrosine phosphorylation in mouse spleen cells and in the mouse WEHI-231 B- cell lymphoma was investigated. We have confirmed previous studies which showed that exposure to high levels (several hundred

microM) of mercury lead to very large increases in the level of protein tyrosine phosphorylation in these cell systems. However we have also demonstrated that low levels (in the order of 0.1 to 1.0 microM) of mercury also significantly upregulate protein tyrosine phosphorylation. Mercury induced protein tyrosine phosphorylation is inhibited by the mercury chelator penicillamine and by pretreating treating target cells with the sulfhydryl blocking reagent N- hydroxymaleimide. These results suggest that exposure to low levels of mercury could potentially interfere with lymphocyte signal transduction and so offer a possible explanation as to how mercury exposure could lead to immune cellular dysfunction. On a molecular level, the results suggest that the site(s) of action with respect to mercury dependent induction of protein tyrosine phosphorylation is likely a free disulfide group or groups located on the outer leaflet of the plasma membrane.

156. NHMRC WORKING PARTY 1999

Amalgams should not be used in: pregnant women, breast feeding women, children under 6 years, people with kidney disorders, neurological problems, retrograde root-canal fillings, as cores underneath metal based crowns, in conjunction with other metals in the mouth, people with diagnosed lichen planus, and people with compromised immune systems.

157. DENTAL AMALGAMS AND HEAVY METALS: WHAT RISKS FOR HEALTH AND THE ENVIRONMENT. COLLOQUIUM ORGANISED BY THE GREEN GROUP IN THE EUROPEAN PARLIAMENT - 7 AND 8 JANUARY 1999 - EUROPEAN PARLIAMENT - LUXEMBOURG BRUSSELS, 19 JANUARY 1999

A not insignificant number of people are likely to suffer from the presence of amalgams in their mouths (allergic reactions, problems in the central nervous system, disruption of the immune and hormonal systems); Foetuses and young children are particularly at risk, mercury crosses the placenta and accumulates in the organs of the child; The insidious chronic effects on the cells, membranes and enzymes in the organism are difficult to quantify and necessitate recourse to tests and specific analyses in most instances neglected by official bodies. The problems of electro-galvanism provoked as a result of the presence of several metals in the mouth can be aggravating factors.

In addition, emphasis was placed on the insufficient amount of data available on alternatives to amalgams. Other dental materials, metal or plastic, can lead to phenomenon and even auto-immune reactions of which the impose negative effects do not seem to be comparable to in their magnitude and frequency to those of amalgams.

158. MERCURY: GOD OF TH2 CELLS,1995, P.W. MATHIESON, CLINICAL EXP IMMUNOL.,102(2):229-30

159. MERCURIC CHLORIDE-INDUCED APOPTOSIS IS DEPENDENT ON PROTEIN SYNTHESIS. GOERING PL, THOMAS D, ROJKO JL, LUCAS AD. TOXICOL LETT 1999; 105(3): 183-95;

160. PRESENCE OF MICRONUCLEI IN LYMPHOCYTES OF MERCURY EXPOSED WORKERS', IMMUNOPHARMACOL IMMUNOTOXICOL, 1999, 21(1):141-50 NEUROIMMUNOTOXICOLOGY:

161. HUMORAL ASSESMENT OF NEUROTOXICITY AND AUTOIMMUNE MECHINISMS. EL-FAWAI HA, WATERMAN SJ, DE FEO A, SHAMY MY. CONTACT DERMATITIS 1999; 41(1): 60-1.

162. Genetic and Environmental Factors Contributing to the Onset of Allergic Disorders.Brugnolo F, Sampognaro S, Maggi E. Int Arch Allergy Immunol 2000 Jan;121(1):2-9.

163. Immune function of bovine leukocytes after in vitro exposure to selected heavy metals. De Guise S Bernier J Lapierre P Dufresne MM Dubreuil P Fournier M Am J Vet Res (2000 Mar) 61(3):339-44

OBJECTIVE: To study effects of in vitro exposure of bovine leukocytes to mercury, cadmium, and lead on phagocytosis, natural killer cell activity, and lymphocyte proliferation. SAMPLE POPULATION: Leukocytes from 6 nonpregnant Holstein heifers. PROCEDURE: Leukocytes were exposed in vitro to the aforementioned metals, and leukocyte functions were assessed. RESULTS: Phagocytosis was suppressed by 10(- 5) to 10(-7) M CdCl2 and by 10(-5) and 10(-6) M HgCl2, but not 10(-7) M HgCl2 nor 10(-4) to 10(-6) M PbCl2. Spontaneous and concanavalin A-or phytohemagglutinin-stimulated proliferation of metal-treated bovine blood mononuclear cells was not significantly different from that of nontreated control cells, except for enhanced spontaneous proliferation in response to 10(-5) M HgCl2. When proliferation was expressed as a stimulation index, a dose-dependent increase of spontaneous proliferation was observed in response to exposure to HgCl2 and PbCl2. Compared with response to 10(-6) or 10(-7) M CdCl2, reduction of mitogen-induced and spontaneous proliferation was observed on exposure to 10(-5) M CdCl2. Natural killer cell activity against YAC-1 target cells, evaluated by flow cytometry, was decreased only in cells exposed to 10 M HgCl2. CONCLUSION AND CLINICAL RELEVANCE: Bovine leukocytes are susceptible to the immunomodulatory effects of in vitro exposure to heavy metals at concentrations equal to or higher than those at which similar effects are seen for leukocytes from most other animal species for which data are available for comparison. Exception is phagocytosis, which is severely affected by low concentrations of CdCl2 and HgCl2 in cattle. Reduction of defense mechanisms on exposure to metals could lead to increased susceptibility to potential pathogens.

164. Detection of the effects of repeated dose combined propoxur and heavy metal exposure by measurement of certain toxicological,haematological and immune function parameters in rats. Institoris L Siroki O Undeger U Basaran N Banerjee BD Desi I Toxicology (2001 Jun 21) 163(2-3):185-93

In the present study, an immunotoxicity test system, containing general toxicological (body weight gain, organ weights), haematological (WBC,RBC, Ht, mean cell volume of the RBCs, cell content of the femoral bone marrow), and immune function (PFC assay, DTH reaction) investigations, was used for detection the effects of a 4 weeks repeated low dose combined oral exposure of male Wistar ratswith propoxur and the heavy metals arsenic or mercury. Two doses of the compounds were used: a higher one (the lowest dose which resulted in significant change of at least one parameter examined in previous dose-effect experiments), and a lower one (the highest dose which proved to be non-effective). The applied doses were: 8.51 and 0.851 mg kg(-1) of propoxur, 13.3 and 3.33 mg kg(-1) of NaAsO(2), and 3.20 and 0.40 mg kg(-1) of HgCl(2). In the combination treatment, the high dose of propoxur was combined with the low dose of arsenic or mercury, and the high doses of each heavy metals were combined with the low dose of propoxur. The main finding of this study was thatsome of the combinations significantly altered the relative weight of liver, adrenals and kidneys, related to both the untreated and the high dose internal control. Among the immune functions examined,

only the PFC content of the spleen showed a trend of changes in certain combinations versus the corresponding high dose control. According to the present results, combined exposure with propoxur and the heavy metals examined can modify the detection limit of the single compounds and/or may alter their toxic effects.

165. GENETIC CONTROL OF RESISTANCE TO MERCURY-INDUCED IMMUNE/AUTOIMMUNE ACTIVATION. ABEDI-VALUGERDI M Hansson M Moller G Scand J Immunol (2001 Jul-Aug) 54(1-2):190-7

Previous studies have shown that genetic factors control the susceptibility to mercury-induced immunoglobulin (Ig)G1 antibody formation, IgE synthesis, renal IgG deposits and antinucleolarauto antibodies (ANolA) production in the susceptible mice. In this study, we examined the genetic control of resistance to these characteristics after HgCl2 injection in F1 hybrid crosses between the highly mercury resistant DBA/2 and mercury susceptible NZB (H-2d), SJL (H-2 s), A.CA (H-2f) and DBA/1 (H-2q) mice and also in backcross hybrids between (DBA/2 x SJL)F1 and SJL mice. We observed that mercury-induced immune/autoimmune manifestations were profoundly down regulated in most (if not all) of the F1 hybrids, indicating that the resistance to mercury was a dominant trait. Analysis of mercury-induced immune/autoimmune responses in the (DBA/2 x SJL) x SJL backcross hybrids suggested that only one gene or a cluster of genes determined the resistance to the ANolA production, whereas the resistance to other characteristics was controlled by two and/or three gene loci. By H-2 genotyping the backcross mice, it was found that H-2d haplotype per se could confer resistance to ANolA production. However, we did not find any significant association between the H-2d haplotype and the resistance to increase of IgG1 and IgE synthesis and the development of renal IgG1 deposits. Thus, while in DBA/2 mice, gene(s) in the H-2 loci strictly contribute to the inheritance of resistance to ANolA production; non-H-2 genes mainly govern the inheritance of unresponsiveness regarding other characteristics.

166. ANALYSIS OF MERCURY-INDUCED IMMUNE ACTIVATION IN NONOBESE DIABETIC (NOD) MICE. BRENDEN N RABBANI H Abedi-Valugerdi M Clin Exp Immunol (2001 Aug) 125(2):202-10

In susceptible mice, the heavy metal ion mercury is able to induce a strong immune activation, which resembles a T helper 2 (Th2) type of immune response and is characterized by a polyclonal B cell activation, formation of high levels of IgG1 and IgE antibodies, production of autoantibodies of different specificities and development of renal IgG deposits. In the present study, we analysed the in vivo effects of mercury in nonobese diabetic (NOD) mice, which is believed to develop a spontaneous Th1 cell-mediated autoimmune diabetes similar to type 1 diabetes in humans. Three weeks of treatment with mercury induced a strong Th2 like immune/autoimmune response in NOD mice. This response was characterized by an intensive increase in splenic IgG1 antibody secreting cells, a marked elevation in serum IgE levels, a substantial increase in splenic IL-4 mRNA, but a significant decrease in splenic IFN-gamma mRNA. Mercury-induced IgG1 antibodies were mainly against ssDNA, TNP and thyroglobulin, but not against nucleolar antigen. Moreover, mercury-injected NOD mice developed high titres of IgG1 deposits in the kidney glomeruli. We further tested if the generated Th2 response could interfere with the development of insulitis and diabetes in NOD mice. We found that three weeks of treatment with mercury was also able to significantly suppress the development of insulitis and postpone the onset of diabetes in these mice. Thus, mercury-induced immune activation can counter-regulate the Th1 cell-mediated autoimmune responses and confer a partial protection against autoimmune diabetes in NOD mice.

167. IMMUNE FUNCTION, STRESS RESPONSE, AND BODY CONDITION IN ARCTIC-BREEDING COMMON EIDERS IN RELATION TO CADMIUM, MERCURY, AND SELENIUM CONCENTRATIONS. WAYLAND M GILCHRIST HG MARCHANT T KEATING J SMITS JE ENVIRON RES (2002 SEP) 90(1):47-60

We examined relationships between trace metal concentrations in tissues of common eider ducks (cadmium, mercury, and selenium) and selected biomarkers of health (stress response, immune function, and body condition). This study was conducted at an eider nesting colony in the Canadian arctic in 1998 and 1999. Capture-induced stress, measured as the rise in corticosterone concentrations following capture, was positively related (P=0.03) to renal cadmium concentration in 1998 when incubating eiders were sampled, but not in 1999 when prenesting eiders were sampled. Stress response was inversely related (P=0.02) to selenium concentrations in 1999. Following capture and blood sampling in 1999, eiders were placed in a flight pen on-site for eight days in order to examine immune function. Cell-mediated immunity, measured as the skin-swelling response to an intradermal injection of phytohemagglutinin-P, (PHA- P), was positively related (P=0.003) to hepatic selenium. The heterophil:lymphocyte ratio was inversely related (P=0.08) to hepatic selenium. In 1998, selenium was positively related to body mass (P=0.01), abdominal fat mass (P=0.07), kidney mass (P=0.03), and liver mass (P=0.07). In 1999, hepatic mercury was negatively relatedto abdominal fat mass (P=0.01), spleen mass (P=0.07) and body mass at capture (P=0.09) in prenesting eiders.

168. MERCURY EXPOSURE DURING IMMUNE APHERESIS. BAUER E SCHAFFER A KRAMER L DERFLER K THER APHER DIAL (2005 OCT) 9(5):A38

Background: Immunoadsorption using protein A columns is increasingly used for selective extracorporeal removal of circulating antibodies and autoantibodies. Current apheresis systems employ reusable columns requiring long-term storage (20-50 treatment sessions). To prevent microbial growth during storage, columns are primed with ethyl mercury thiosalicylic acid (thiomerosal, .01% solution) for storage and rinsed with phosphate buffer before use. Aims: To test the hypothesis of a substantial mercury exposure in protein A immunoadsorption and to investigate the effect of adding N-acetylcysteine to the rinsing solution. Patients and Methods: Whole blood mercury levels were measured by atomic absorption spectroscopy (hydride method) before and after protein A immunoadsorption (11 patients, 26 treatments), anti-IgG-immunoadsorption (8 patients, 13 treatments) and LDL apheresis (DALI and Therasorb systems; 9 patients, 14 treatments). Results: Protein A immune apheresis treatment significantly increased blood mercury levels from a median of 5.4 microg/L (range, 1.4-37.6, normal, <5 microg/L) to 23.7 microg/L, (range 7.2-107, P < 0.001). Baseline mercury levels were normal in treatment-naive patients but gradually increased on regular treatment. In a single patient with excessive mercury levels (107 microg/L), neurologic toxicity (intention tremor) occurred during immune apheresis. In the other groups blood mercury levels were not different from healthy controls. Adding N-acetylcysteine to the rinsing solution lead to a significant decrease in mercury exposure during protein A apheresis treatment. Discussion: This preliminary report suggests that mercury toxicity may develop in patients on regular protein A immune apheresis treatment. Given impaired renal function in many patients, any effort should be undertaken to reduce systemic mercury exposure, either by adding chelators to the rinsing solution or ideally by replacement of thiomerosal. Adding N-acetylcysteine significantly reduced mercury exposure, so that we now routinely rinse protein A columns with N-acetylcysteine before use.

169. BAUER E SCHAFFER A KRAMER L DERFLER K MERCURY EXPOSURE DURING IMMUNE APHERESIS. THER APHER DIAL (2005 OCT) 9(5):A38

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170. MICROARRAY ANALYSIS OF MERCURY-INDUCED CHANGES IN GENE EXPRESSION IN HUMAN LIVER CARCINOMA (HEPG2) CELLS: IMPORTANCE IN IMMUNE RESPONSES. AYENSU WK TCHOUNWOU PB INT J ENVIRON RES PUBLIC HEALTH (2006 JUN) 3(2):141-73

Mercury is widely distributed in the biosphere, and its toxic effects have been associated with human death and several ailments that include cardiovascular diseases, anemia, kidney and liver damage, developmental abnormalities, neurobehavioral disorders, autoimmune diseases, and cancers in experimental animals. At the cellular level, mercury has been shown to interact with sulphydryl groups of proteins and enzymes, to damage DNA, and to modulate cell cycle progression and/or apoptosis. However, the underlying molecular mechanisms of mercury toxicity remain to be elucidated. Our laboratory has demonstrated that mercury exposure induces cytotoxicity and apoptosis, modulates cell cycle, and transcriptionally activates specific stress genes in human liver carcinoma cells. The liver is one of the few organs capable of regeneration from injury. Dormant genes in the liver are therefore capable of reactivation. In this research, we hypothesize that mercury-induced hepatotoxicity is associated with the modulation of specific gene expressions in liver cells that can lead to several disease states involving immune system dysfunctions. In testing this hypothesis, we used an Affymetrix

oligonucleotide microarray with probe sets complementary to more than 20,000 genes to determine whether patterns of gene expressions differ between controls and mercury (1-3 microg/mL) treated cells. There was a clear separation in gene expression profiles between controls and mercury-treated cells. Hierarchical cluster analysis identified 2,211 target genes that were affected. One hundred and eighty-eight of these genes were up-regulated, among which forty eight were significant (p = 0.001) with greater than a two-fold change difference in the concentration range (1-3 microg/mL) of mercury-treated cells; twelve genes were moderately over-expressed with an increase of more than one fold (p = 0.004). 2,023 genes were down- regulated with only forty of them reaching statistically significant decline at p = 0.05 according to the Welch's ANOVA/Welch's t-test. Further analyses of affected genes identified genes located on all human chromosomes with higher than normal effects on genes found on chromosomes 1-14, 17-20 (sex-determining region Y)-box18SRY, 21 (splicing factor, arginine/serine-rich 15 and ATP-binding), and X (including BCL6-co-repressor). These genes are categorized as control and regulatory genes for metabolic pathways involving the cell cycle (cyclin-dependent kinases), apoptosis, cytokine expression, Na+/K+ ATPase, stress responses, G-protein signal transduction, transcription factors, DNA repair as well as metal-regulatory transcription factor 1, MTF1 HGNC, chondroitin sulfate proteoglycan 5 (neuroglycan C), ATP-binding cassette, sub-family G (WHITE), cytochrome b-561 family protein, CDC-like kinase 1 (CLK1 HGNC) (protein tyrosine kinase STY), Na+/H+ exchanger regulatory factor (NHERF HGNC), potassium voltage-gated channel subfamily H member 2 (KCNH2), putative MAPK activating protein (PM20, PM21), ras homolog gene family, polymerase (DNA directed), delta regulatory subunit (50 kDa), leptin receptor involved in matopoietin/interferon-class (D200- domain) cytokine receptor activity and thymidine kinase 2, mitochondrial TK2 HGNC and related genes. Significant alterations in these specific genes provide new directions for deeper mechanistic investigations that would lead to a better understanding of the molecular basis of mercury-induced toxicity and human diseases that may result from disturbances in the immune system.

171. IMMUNE FUNCTION EFFECTS OF DENTAL AMALGAM IN CHILDREN: A RANDOMIZED CLINICAL TRIAL. SHENKER BJ MASEREJIAN NN ZHANG A MCKINLAY S J AM DENT ASSOC (2008 NOV) 139(11):1496-505

BACKGROUND: Dental amalgam is a widely used restorative material containing 50 percent elemental mercury that emits mercury vapor. No randomized clinical trials have determined whether there are adverse immunological effects associated with this low-level mercury exposure in children. The objective of this study was to evaluate a subpopulation of the participants in the New England Children's Amalgam Trial for in vitro manifestations of immunotoxic effects of dental amalgam. METHODS: The authors conducted a randomized clinical trial in which children requiring dental restorative treatment were randomly assigned to receive either amalgam for posterior restorations or resin-based composite restorations. They assessed 66 children, aged 6 to 10 years, for total white blood cell counts, specific lymphocyte (T-cell and B-cell) counts and lymphocyte, neutrophil and monocyte responsiveness across a five-year period. Because of the small number of participants, the authors acknowledge that the study is exploratory in nature and has limited statistical power. RESULTS: The mean number of tooth surfaces restored during the five-year period was 7.8 for the amalgam group and 10.1 for the composite group. In the amalgam group, there was a slight, but not statistically significant, decline in responsiveness of T cells and monocytes at five to seven days after treatment; the authors consistently observed no differences at six, 12 or 60 months.

CONCLUSIONS: The findings of this study confirm that treatment of children with amalgam restorations leads to increased, albeit low- level, exposure to mercury. In this exploratory analysis of immune function, amalgam exposure did not cause overt immune deficits, although small transient effects were observed five to seven days after restoration placement. CLINICAL IMPLICATIONS: These findings suggest that immunotoxic effects of amalgam restorations are minimal and transient in children and most likely do not need to be of concern to practitioners considering the use of this restorative dental material.

172. DAS K SIEBERT U GILLET A DUPONT A DI-POI C FONFARA S MAZZUCCHELLI G DE PAUW E DE PAUW-GILLET MC MERCURY IMMUNE TOXICITY IN HARBOUR SEALS: LINKS TO IN VITRO TOXICITY. ENVIRON HEALTH (2008) 7:52

BACKGROUND: Mercury is known to bioaccumulate and to magnify in marine mammals, which is a cause of great concern in terms of their general health. In particular, the immune system is known to be susceptible to long-term mercury exposure. The aims of the present study were (1) to determine the mercury level in the blood of free- ranging harbour seals from the North Sea and (2) to examine the link between methylmercury in vitro exposure and immune functions using seal and human mitogen-stimulated peripheral blood mononuclear cells (T-lymphocytes). METHODS: Total mercury was analysed in the blood of 22 harbour seals. Peripheral blood mononuclear cells were isolated from seals (n = 11) and from humans (n = 9). Stimulated lymphocytes of both species were exposed to functional tests (proliferation, metabolic activity, radioactive precursor incorporation) under increasing doses of methylmercury (0.1 to 10 microM). The expression of cytokines (IL-2, IL-4 and TGF-beta) was investigated in seal lymphocytes by RT-PCR and by real time quantitative PCR (n = 5) at methylmercury concentrations of 0.2 and 1 microM. Finally, proteomics analysis was attempted on human lymphocytes (cytoplasmic fraction) in order to identify biochemical pathways of toxicity at concentration of 1 microM (n = 3). RESULTS: The results showed that the number of seal lymphocytes, viability, metabolic activity, DNA and RNA synthesis were reduced in vitro, suggesting deleterious effects of methylmercury concentrations naturally encountered in free-ranging seals. Similar results were found for human lymphocytes. Functional tests showed that a 1 microM concentration was the critical concentration above which lymphocyte activity, proliferation and survival were compromised. The expression of IL-2 and TGF-beta mRNA was weaker in exposed seal lymphocytes compared to control cells (0.2 and 1 microM). Proteomics showed some variation in the protein expression profile (e.g. vimentin). CONCLUSION: Our results suggest that seal and human PBMCs react in a comparable way to MeHg in vitro exposure with, however, larger inter-individual variations. MeHg could be an additional cofactor in the immunosuppressive pollutant cocktail generally described in the blood of seals and this therefore raises the possibility of additional additive effects in the marine mammal immune system.

173. COMPROMISED IMMUNE COMPETENCE IN FREE-LIVING TREE SWALLOWS EXPOSED TO MERCURY. HAWLEY DM HALLINGER KK CRISTOL DA ECOTOXICOLOGY (2009 JUL) 18(5):499-503

Mercury is a pervasive environmental contaminant and a well- documented immunosuppressor. However, little is known about the effects of mercury

contamination on health of free-living vertebrate populations. The South River in Virginia, USA was heavily contaminated with industrial mercury from 1929 to 1950, and recentstudies have documented high levels of circulating mercury in riparian songbirds breeding below the site of contamination. Here we used two standardized immune assays, mitogen-induced swelling in response to phytohaemagglutinin (PHA) and antibody response to sheep red blood cells (SRBCs), to test for effects of mercury toxicity on the immune system of female tree swallows (Tachycineta bicolor) which feed on terrestrial and aquatic insects along the contaminated waterway. We found that females breeding at mercury-contaminated sites mounted significantly weaker PHA-induced swelling responses than those at reference sites in both years of study. However, among females on the contaminated sites, individual bloodstream mercury concentration did not predict the extent of mitogen-induced swelling. We did not detect any differences between reference and contaminated females in the strength of antibody responses to SRBCs, but sample sizes for this assay were significantly smaller. Overall, our results suggest that mercury toxicity can exert sub-lethal immunosuppression in free-living, insectivorous songbirds. The potential fitness consequences of the detected differences in immunocompetence caused by mercury toxicity warrant further study.

174. LUBICK N MERCURY ALTERS IMMUNE SYSTEM RESPONSE IN ARTISANAL GOLD MINERS. ENVIRON HEALTH PERSPECT (2010 JUN) 118(6):A243

175. LASER ABLATION ICP-MS CO-LOCALIZATION OF MERCURY AND IMMUNE RESPONSE IN FISH. BARST BD GEVERTZ AK CHUMCHAL MM SMITH JD RAINWATER TR DREVNICK PE HUDELSON KE HART A VERBECK GF ROBERTS AP ENVIRON SCI TECHNOL (2011 OCT 15) 45(20):8982-8

Mercury (Hg) contamination is a global issue with implications for both ecosystem and human health. In this study, we use a new approach to link Hg exposure to health effects in spotted gar (Lepisosteus oculatus) from Caddo Lake (TX/LA). Previous field studies have reported elevated incidences of macrophage centers in liver, kidney, and spleen of fish with high concentrations of Hg. Macrophage centers are aggregates of specialized white blood cells that form as an immune response to tissue damage, and are considered a general biomarker of contaminant toxicity. We found elevated incidences of macrophage centers in liver of spotted gar and used a new technology for ecotoxicology studies, laser ablation-inductively coupled plasma- mass spectrometry (LA-ICP-MS), to colocalize aggregates and Hg deposits within the tissue architecture. We conclude that Hg compromises the health of spotted gar in our study and, perhaps, other fish exposed to elevated concentrations of Hg.

176. LEWIS CA CRISTOL DA SWADDLE JP VARIAN-RAMOS CW ZWOLLO P DECREASED IMMUNE RESPONSE IN ZEBRA FINCHES EXPOSED TO SUBLETHAL DOSES OF MERCURY. ARCH ENVIRON CONTAM TOXICOL (2013 FEB) 64(2):327-36

Mercury (Hg) is a ubiquitous contaminant with deleterious effects on many wildlife species. Most studies to date have focused on fish- eating birds and mammals because much historical Hg pollution is aquatic. Recently, however, comparable blood-Hg levels have been found in terrestrial insectivorous songbirds. As a result, research is needed to clarify the effects of Hg exposure on songbirds. One fundamental end point that is still poorly understood is the effect of Hg on the songbird immune system. If Hg affects the functioning of the immune system, exposed songbirds may be less able to mount an

appropriate immune response against invading pathogens. To gain insight into how Hg affects songbird immune function on a cellular level, a flow cytometric assay was developed to measure lipopolysaccharide-induced B-lymphocyte proliferation in zebra finches (Taeniopygia guttata). This is the first experimental (dosing) study of the potential effect of Hg on songbird immune system functioning. Decreased B cell proliferation was observed after lipopolysaccharide exposure in individuals with greater concentrations of Hg in their blood and tissues. In addition, these individuals had decreased ratios of proliferating-to-resting B cells. This decrease in lymphocyte proliferation in response to an effective mitogen suggests that environmental exposure to sublethal levels of Hg may inhibit or delay B cell proliferation in songbirds, potentially increasing susceptibility to disease and decreasing survivorship.

177. SINGARAM G HARIKRISHNAN T CHEN FY BO J GIESY JP MODULATION OF IMMUNE-ASSOCIATED PARAMETERS AND ANTIOXIDANT RESPONSES IN THE CRAB (SCYLLA SERRATA) EXPOSED TO MERCURY. CHEMOSPHERE (2013 JAN) 90(3):917-28

Organic and inorganic contaminants can suppress immune function in molluscs and crustaceans. It was postulated that metals could modulate immune function in marine crabs. To test this hypothesis, sublethal effects of mercury (Hg) on cellular immune and biochemical responses of crabs were determined. When crabs were exposed for 14 d to environmentally-relevant concentrations of Hg, changes in immune- associated parameters including, total haemocyte count, lysosomal membrane stability, phenoloxidase, super oxide generation and phagocytosis were observed. Oxidative stress, as measured by lipid peroxidation, antioxidant responses, including superoxide dismutase and catalase activities and glutathione-mediated antioxidant enzymes in serum, haemocyte lysate, gills, hepatopancreas and muscle were assessed in crabs exposed to Hg. Exposure to Hg resulted in significantly lesser immune-associated parameters in haemolymph and antioxidants in all tissues studied. Conversely, GST and phenoloxidase activity, were greater in crabs exposed to Hg. Responses of antioxidant parameters (SOD, CAT and GP(x)) were positively correlated with immune responses, including THC, superoxide and phagocytosis. These results were postulated to be due to an immediate response of antioxidant defense to oxygen radicals generated. Overall, the results suggest that 14 d exposure to environmentally realistic concentrations of Hg causes immunomodulation and potentially harmful lessened antioxidant defenses of crabs.