Amyl Nitrites (Poppers)

Acute haemolytic anaemia after inhalation of amyl nitrite

Tracey D Graves, *BSc MRCP* and Sheena Mitchell, *FRCP*

http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=14645612

1: Am J Med. 1985 May;78(5):811-6.

Volatile nitrites. Use and adverse effects related to the current epidemic of the acquired immune deficiency syndrome.

Newell GR, **Mansell PW**, **Spitz MR**, **Reuben JM**, **Hersh EM**.

Early reports of the acquired immune deficiency syndrome (AIDS) in homosexual men suggested that the cause might be related to homosexual life-style practices, including use of recreational drugs. Inhalation of volatile nitrites is a possible contributing factor in AIDS because their pharmacologic properties lead to toxicity. Metabolism of N-nitroso compounds produces mutagens, teratogens, and potent carcinogens in 39 different animal species, and volatile nitrites have deleterious effects on human lymphocytes in vitro and in vivo. In relation to the current AIDS epidemic, the timing of production and sales of volatile nitrites for recreational use is the only new life-style factor that might answer the question "why AIDS now?" Prevalence of nitrite use among male homosexuals is very high, and almost every reported case of Kaposi's sarcoma during the past three years includes a history of prior nitrite use. The age of the group of patients in whom Kaposi's sarcoma and AIDS are developing is consistent with a cohort initially exposed seven to 10 years ago. Cessation of nitrite use could reduce the epidemic.

Antibiotics:

Chemical agents and the immune response.

M I Luster and G J Rosenthal

http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1519592&blobtype=pdf

Minocycline and autoimmunity.

Eichenfield AH.

Division of Pediatric Rheumatology, Mount Sinai School of Medicine, New York, New York 10029-6574, USA.

Minocycline is the most widely prescribed systemic antibiotic for the management of acne. In the past several years, increasing attention has been paid to the drug, both for its potential use as a disease-modifying antirheumatic agent and for its propensity to engender untoward

autoimmune reactions, including serum sickness-like disease, drug-induced lupus, and autoimmune hepatitis. This paper reviews the evidence for minocycline as an anti-inflammatory and immunomodulatory agent, its utility in the treatment of rheumatoid arthritis, and the spectrum of adverse reactions that have been ascribed to the drug in the past 5 years.

Minocycline-induced autoimmune syndromes: an overview.

Elkayam O, **Yaron M**, **Caspi D**.

Department of Rheumatology, Tel Aviv Sourasky Medical Center, The Sackler Faculty of Medicine, University of Tel Aviv, Israel.

OBJECTIVE: To increase awareness of minocycline-induced autoimmune syndromes. METHODS: Review of relevant publications from the American and European literature. RESULTS: Four minocycline-induced syndromes have been described in 82 patients: serum sickness, drug-induced lupus, autoimmune hepatitis, and vasculitis. Aside from sporadic cases of serum sickness, all other syndromes occurred in patients treated for acne. Drug-induced lupus and hepatitis were by far the most common events (66 cases). Except for serum sickness, which presented shortly (mean, 16 days) after minocycline, the autoimmune syndromes manifested after protracted use (mean, 25.3 months). As expected, the patients with acne were young (mean, 19.7 years). The most frequent symptoms were arthralgia, followed by arthritis, fever, and rash (73, 45, 38, and 29 patients, respectively). Serologically, antinuclear antibodies were the most common finding (63 positive of 68 tests); perinuclear anti-neutrophilic cytoplasmic antibodies (pANCA), when assayed, were similarly frequent (20 of 24 tests). Surprisingly, anti-histone antibodies were uncommon, even among patients with drug-induced lupus (4 of 31 tests). The clinical and serological features of the separate syndromes may overlap. The diagnostic value of pANCA, as well as its possible role in minocycline-induced autoimmunity, are discussed. CONCLUSIONS: Minocycline has the potential to evoke a variety of clinical and serological autoimmune expressions. The number of published reports may underestimate the frequency of this condition, which should be suspected and investigated in young patients with autoimmune manifestations.

Why minocycline can cause systemic lupus - a hypothesis and suggestions for therapeutic interventions based on it.

van Steensel MA.

The tetracycline antibiotic minocycline is widely used in dermatology, but can sometimes cause systemic lupus erythematodes, a serious autoimmune disorder. It is not known how it does this. However, recent data suggest that minocycline can protect cells from apoptosis by inhibition of caspase-dependent and independent cell death pathways. Here, it is suggested that this ability of minocycline is responsible for the induction of lupus. This idea is based on the recent insight that incomplete or failed apoptosis of damaged cells, particularly keratinocytes, may be responsible for the development of auto-immunity. The protection against apoptosis as conferred by minocyclin may be incomplete, with failed apoptosis and development of autoimmunity as a result. Experimental confirmation of the theory may be obtained by in vitro experiments using induction of apoptosis in cell types known to be affected by lupus. Next, mice that are sensitive to apoptosis may be used for in vivo experiments. Novel therapeutic approaches to drug-induced lupus may be based on induction

of apoptosis; DNA-damaging immunosuppressive agents appear particularly useful. Such treatments can be tested in apoptosis-deficient mice that develop autoimmune disease.

Mercury

Activation of the immune system and systemic immune-complex deposits in Brown Norway rats with dental amalgam restorations.

Hultman P, Lindh U, Hörsted-Bindslev P.

http://jdr.iadrjournals.org/cgi/reprint/77/6/1415

Cytokine regulation of a rodent model of mercuric chloride-induced autoimmunity.

L M Bagenstose, P Salgame, and M Monestier

http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=10502547

Mercury-induced autoimmunity in mice.

Jesper Bo Nielsen and Per Hultman

http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=12426151

Mercury exposure, malaria, and serum antinuclear/antinucleolar antibodies in amazon populations in Brazil: a cross-sectional study

Ines A Silva,[1] Jennifer F Nyland,[1] Andrew Gorman,[2] Andre Perisse,[2] Ana Maria Ventura,[3] Elizabeth CO Santos,[3] Jose M de Souza,[3] CL Burek,[1] Noel R Rose,[1] and Ellen K Silbergeld[1]

http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=15522122

Effects of deviating the Th2-response in murine mercury-induced autoimmunity towards a Th1-response

B HÄGGQVIST and P HULTMAN

http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=14616778

Allergic disease, immunoglobulins, exposure to mercury and dental amalgam in Swedish adolescents.

Herrström P, Högstedt B, Holthuis N, Schütz A, Råstam L.

High-dose exposure to inorganic mercury in man can influence the immune system and in rare cases cause immune-related disease. Some experimental animals also react with autoimmunity after low doses of inorganic mercury. Glomerulonephritis and an increased formation of immunoglobulin type E (IgE) are characteristic of these reactions. A recent study of 15-year-old adolescents demonstrated an association between immunoglobulin type A (IgA) and mercury concentration in plasma (P-Hg). There was also an association between allergic disease and IgA levels. The present study included 54 male and 23 female 19-year-old students who were recruited from a cohort that had been previously defined in a survey of allergic disease. Of the students, 39 (51%) had asthma, allergic rhinoconjunctivitis or eczema. Similar amalgam burden and P-Hg levels were observed in students with (n = 39) and without (n = 38) allergic disease (P = 0.48 and P = 0.98, respectively). As expected, IgE levels were significantly higher in the group with allergic disease (P = 0.006), but there was no association between P-Hg and IgE. The P-Hg levels were very low (median 1.50 nmol/l) and correlated significantly (r = 0.31) with the small number of amalgam surfaces (P = 0.007). Thirty-seven students had no amalgam fillings. P-Hg levels did not associate significantly with IgA, but did so with IgG2 (r = 0.33; P = 0.003). No conclusive correlation was observed between IgG2 and amalgam fillings. The findings of this study in 19-year-old subjects differ from earlier data obtained in a sample 4 years younger. The possibility of chance in the association between P-Hg levels and IgG2 must, however, be considere.

Mechanism of mercury-induced autoimmunity: both T helper 1- and T helper 2-type responses are involved.

Hu H, **Möller G**, **Abedi-Valugerdi M**.

Department of Immunology, Arrhenius Laboratories for Natural Sciences, Stockholm University, Stockholm, Sweden.

Mercury can induce a systemic autoimmune disease in susceptible mouse strains. H-2s mice are particularly susceptible to mercury-induced autoimmunity and other mouse strains are more or less resistant. T helper 1/T helper 2 (Th1/Th2) dichotomy has been proposed for resistance or susceptibility, respectively. In the current study we show that mercury treatment induced a full autoimmune response in both C57BL/6 (H-2b) wild-type and interleukin-4 (IL-4)-deficient mice. Antibody production of all isotypes were induced, except that in IL-4-deficient mice there was no immunoglobulin E (IgE) and very low levels of immunoglobulin G1 (IgG1) antibody synthesis. Autoantibodies of different specificities were produced. The granular pattern of all IgG subclasses deposits were detected in the kidneys. In contrast to mercury-treated H-2s seconds mice, we did not detect any anti-nucleolar autoantibodies in the sera of mercury-treated wild-type or IL-4-deficient mice. To further explore the role of Th1/Th2 cytokines in the mercury model, we performed anti-interferon-gamma antibody treatment in IL-4-deficient mice together with mercury treatment and found that the production of IgG2a and IgG3, but not IgG2b, antibodies was downregulated. This indicated that besides Th2-type cytokines, Th1-type and other cytokines were involved as well in mercury-induced autoimmune response. Thus, C57BL/6 mice with H-2b genotype are highly susceptible to mercury-induced autoimmunity, and the genetic susceptibility to mercury involves more than a predisposition of a Th1-or Th2-type response.

Activation of the immune system and systemic immune-complex deposits in Brown Norway rats with dental amalgam restorations.

Hultman P, **Lindh U**, **Hörsted-Bindslev P**.

Department of Health and Environment, Linköping University, Sweden.

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.

The beneficial effect of amalgam replacement on health in patients with autoimmunity.

Prochazkova J, **Sterzl I**, **Kucerova H**, **Bartova J**, **Stejskal VD**.

The Institute of Dental Research 1st Medical Faculty Charles University and General University Hospital, Prague, Czech Republic. prochazkova@vus.cz

BACKGROUND: Patients with certain autoimmune and allergic diseases, such as systemic lupus, multiple sclerosis, autoimmune thyroiditis or atopic eczema, often show increased lymphocyte stimulation by low doses of inorganic mercury in vitro. The patients often report clinical metal hypersensitivity, especially to nickel. OBJECTIVE AND METHODS: In this study we examined the health impact of amalgam replacement in mercury-allergic patients with autoimmunity. The suitability of MELISA, an optimized lymphocyte stimulation test, for the selection of susceptible patients and monitoring of sensitization was also examined. Amalgam fillings were replaced with composites and ceramic materials. Follow-up health status and lymphocyte reactivity were assessed and evaluated half a year or later following amalgam removal. RESULTS: Results of lymphocyte reactivity measured with MELISA indicate that in vitro reactivity after the replacement of dental amalgam decreased significantly to inorganic mercury, silver, organic mercury and lead. Out of 35 patients, 25 patients (71%) showed improvement of health. The remaining patients exhibited either unchanged health (6 patients, 17%) or worsening of symptoms (4 patients, 11%). The highest rate of improvement was observed in patients with multiple sclerosis, the lowest rate was noted in patients with eczema. The initial mercury-specific lymphocyte reactivity was significantly higher in the responder group, than in the non-responders, whose health was not improved by amalgam removal. All patients with health improvement after amalgam replacement showed reduced proliferation to inorganic mercury in follow-up MELISA. In vitro responses to phenylmercury and nickel did not differ between the groups.

CONCLUSIONS: Mercury-containing amalgam may be an important risk factor for patients with autoimmune diseases. MELISA is a valuable tool for selection of patients for amalgam replacement and also for monitoring of metal allergies.

Cytokine regulation of a rodent model of mercuric chloride-induced autoimmunity.

Bagenstose LM, **Salgame P**, **Monestier M**.

Department of Microbiology and Immunology, Temple University School of Medicine, Philadelphia, PA 19140, USA.

Experimental models of chemically induced autoimmunity have contributed to our understanding of the development of autoimmune diseases in humans. Heavy metals such as mercury induce a dramatic activation of the immune system and autoantibody production in genetically susceptible rats and mice. This autoimmune syndrome is dependent on T cells, which are important for B-cell activation and cytokine secretion. Several studies have focused on the roles of T-helper (Th)1 and Th2 cells and their respective cytokines in the pathogenesis of mercury-induced disease. This article reviews recent studies that have examined the patterns of cytokine gene expression and where investigators have manipulated the Th1 and Th2 responses that occur during mercury-induced autoimmunity. Finally, we will discuss some biochemical/molecular mechanisms by which heavy metals may induce cytokine gene expression.

Effects of mercury on human polymorphonuclear leukocyte function in vitro.

J. Contrino, P. Marucha, R. Ribaudo, R. Ference, P. E. Bigazzi, and D. L. Kreutzer

http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=3394794

The in vitro effects of mercury on peritoneal leukocytes (PMN and macrophages) from inbred brown Norway and Lewis rats.

Contrino J, **Kosuda LL**, **Marucha P**, **Kreutzer DL**, **Bigazzi PE**.

The present paper demonstrates that HgCl2 can affect rat peritoneal polymorphonuclear leukocyte (PMN) and macrophage (M phi) functions in vitro. In addition, we have noticed that these effects of mercury vary according to the rat strain: for example, HgCl2 stimulates H2O2 release from Lewis (LEW) but not Brown Norway (BN) PMN. Similarly, LEW M phi produce high levels of H2O2 when exposed to HgCl2 in vitro, whereas BN M phi do not. Finally, mercury inhibits erythrophagocytosis of both LEW and BN "resident" peritoneal M phi. Preliminary experiments using M phi from other rat strains have also shown that MAXX M phi are stimulated by HgCl2 to release H2O2 in vitro, whereas Yoshida M phi are inhibited. Differences in lymphocyte responses (e.g. delayed-type hypersensitivity reactions and mitogen stimulation) between rats of various strains are well known. To these examples one may now add variations in PMN and M phi responses to mercury and possibly other metals. Our results suggest that caution should be exercised in interpreting the outcome of immunotoxicity studies in experimental animals. In particular, outbred rats may not provide appropriate models, that might be better obtained by comparative investigations of rats from various inbred strains.

Vaccine Adjutants:

Immunosuppressive and autoimmune effects of thimerosal in mice.

Havarinasab S, Häggqvist B, Björn E, Pollard KM, Hultman P.

The possible health effects of the organic mercury compound thimerosal (ethylmercurithiosalicylate), which is rapidly metabolized to ethylmercury (EtHg), have recently been much debated and the effect of this compound on the immune system is largely unknown. We therefore studied the effect of thimerosal by treating A.SW (H-2s) mice, susceptible to induction of autoimmunity by heavy metals, with 10 mg thimerosal/L drinking water (internal dose ca 590 microg Hg/kg body weight/day) for up to 30 days. The lymph node expression of IL-2 and IL-15 mRNA was increased after 2 days, and of IL-4 and IFN-gamma mRNA after 6 and 14 days. During the first 14 days treatment, the number of splenocytes, including T and B cells as well as Ig-secreting cells decreased. A strong immunostimulation superseded after 30 days treatment with increase in splenic weight, number of splenocytes including T and B cells and Ig-secreting cells, and Th2- as well as Th-1-dependent serum immunoglobulins. Antinucleolar antibodies (ANoA) targeting the 34-kDa nucleolar protein fibrillarin, and systemic immune-complex deposits developed. The H-2s strains SJL and B10.S also responded to thimerosal treatment with ANoA. The A.TL and B10.TL strain, sharing background genes with the A.SW and B10.S strain, respectively, but with a different H-2 haplotype (t1), did not develop ANoA, linking the susceptibility to H-2. Thimerosal-treated H-2s mice homozygous for the nu mutation (SJL-nu/nu), or lacking the T-cell co-stimulatory molecule CD28 (B10.S-CD28-/-), did not develop ANoA, which showed that the autoimmune response is T-cell dependent. Using H-2s strains with targeted mutations, we found that IFN-gamma and IL-6, but not IL-4, is important for induction of ANoA by thimerosal. The maximum added renal concentration of thimerosal (EtHg) and inorganic mercury occurred after 14 days treatment and was 81 microg Hg/g. EtHg made up 59% and inorganic mercury 41% of the renal mercury. In conclusion, the organic mercury compound thimerosal (EtHg) has initial immunosuppressive effects similar to those of MeHg. However, in contrast to MeHg, thimerosal treatment leads in genetically susceptible mice to a second phase with strong immunostimulation and autoimmunity, which is T-cell dependent, H-2 linked and may at least partly be due to the inorganic mercury derived from the metabolism of ethyl mercury.

Vaccine adjuvants: current state and future trends.

Petrovsky N, Aguilar JC.

The problem with pure recombinant or synthetic antigens used in modern day vaccines is that they are generally far less immunogenic than older style live or killed whole organism vaccines. This has created a major need for improved and more powerful adjuvants for use in these vaccines. With few exceptions, alum remains the sole adjuvant approved for human use in the majority of countries worldwide. Although alum is able to induce a good antibody (Th2) response, it has little capacity to stimulate cellular (Th1) immune responses which are so important for protection against many pathogens. In addition, alum has the potential to cause severe local and systemic side-effects including sterile abscesses, eosinophilia and myofascitis, although fortunately most of the more serious side-effects are relatively rare. There is also community concern regarding the possible role of aluminium in

neurodegenerative diseases such as Alzheimer's disease. Consequently, there is a major unmet need for safer and more effective adjuvants suitable for human use. In particular, there is demand for safe and non-toxic adjuvants able to stimulate cellular (Th1) immunity. Other needs in light of new vaccine technologies are adjuvants suitable for use with mucosally-delivered vaccines, DNA vaccines, cancer and autoimmunity vaccines. Each of these areas are highly specialized with their own unique needs in respect of suitable adjuvant technology. This paper reviews the state of the art in the adjuvant field, explores future directions of adjuvant development and finally examines some of the impediments and barriers to development and registration of new human adjuvants. Copyright 2004 Australasian Society for Immunology Inc.

Arsenic

Unventilated Indoor Coal-Fired Stoves in Guizhou Province, China: Cellular and Genetic Damage in Villagers Exposed to Arsenic in Food and Air

Aihua Zhang,[1] Hong Feng,[1] Guanghong Yang,[1] Xueli Pan,[1] Xianyao Jiang,[1] Xiaoxin Huang,[2] Xuexin Dong,[2] Daping Yang,[2] Yaxiong Xie,[1] Luo Peng,[1] Li Jun,[1] Changjun Hu,[1] Li Jian,[1] and Xilan Wang[1]

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Urinary Trivalent Methylated Arsenic Species in a Population Chronically Exposed to Inorganic Arsenic

Olga L. Valenzuela,[1] Victor H. Borja-Aburto,[2] Gonzalo G. Garcia-Vargas,[3] Martha B. Cruz-Gonzalez,[4] Eliud A. Garcia-Montalvo,[1] Emma S. Calderon-Aranda,[1] and Luz M. Del Razo[1]

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Folate, Homocysteine, and Arsenic Metabolism in Arsenic-Exposed Individuals in Bangladesh

Mary V. Gamble,[1] Xinhua Liu,[2] Habibul Ahsan,[3] J. Richard Pilsner,[1] Vesna Ilievski,[1] Vesna Slavkovich,[1] Faruque Parvez,[1] Diane Levy,[2] Pam Factor-Litvak,[3] and Joseph H. Graziano[1,4]

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Folate and arsenic metabolism: a double-blind, placebo-controlled folic acid–supplementation trial in Bangladesh[1,2,3]

Mary V Gamble, Xinhua Liu, Habibul Ahsan, J Richard Pilsner, Vesna Ilievski, Vesna Slavkovich, Faruque Parvez, Yu Chen, Diane Levy, Pam Factor-Litvak and Joseph H Graziano

http://www.ajcn.org/cgi/content/full/84/5/1093

In Vivo Assessment of Arsenic Bioavailability in Rice and Its Significance for Human Health Risk Assessment

Albert L. Juhasz,[1] Euan Smith,[1] John Weber,[1] Matthew Rees,[2] Allan Rofe,[2] Tim Kuchel,[2] Lloyd Sansom,[3] and Ravi Naidu[1]

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Chemical risks associated with consumption of shellfish harvested on the north shore of the St. Lawrence River's lower estuary.

Fabien Gagnon, Thierry Tremblay, Justine Rouette, and Jacques-François Cartier

http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=15175177

Heavy Metals in the environment:

Metals and kidney autoimmunity.

P E Bigazzi

http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=10502542

Mercury exposure, malaria, and serum antinuclear/antinucleolar antibodies in Amazon populations in Brazil: a cross-sectional study.

Silva IA, **Nyland JF**, **Gorman A**, **Perisse A**, **Ventura AM**, **Santos EC**, **Souza JM**, **Burek CL**, **Rose NR**, **Silbergeld EK**.

BACKGROUND: Mercury is an immunotoxic metal that induces autoimmune disease in rodents. Highly susceptible mouse strains such as SJL/N, A.SW, B10.S (H-2s) develop multiple autoimmune manifestations after exposure to inorganic mercury, including lymphoproliferation, elevated levels of autoantibodies, overproduction of IgG and IgE, and circulating immune complexes in kidney and vasculature. A few studies have examined relationships between mercury exposures and adverse immunological reactions in humans, but there is little evidence of mercury-associated autoimmunity in humans. METHODS: To test the immunotoxic effects of mercury in humans, we studied communities in Amazonian Brazil with well-characterized exposures to mercury. Information was collected on diet, mercury exposures, demographic data, and medical history. Antinuclear and antinucleolar autoantibodies (ANA and ANoA) were measured by indirect immunofluorescence. Anti-fibrillarin autoantibodies (AFA) were measured by immunoblotting. RESULTS: In a gold mining site, there was a high prevalence of ANA and ANoA: 40.8% with detectable ANoA at > or =1:10 serum dilution, and 54.1% with detectable ANA (of which 15% had also detectable ANoA). In a riverine town, where the population is exposed to methylmercury by fish consumption, both prevalence and levels of autoantibodies were lower: 18% with detectable ANoA and 10.7% with detectable ANA. In a reference site with lower mercury exposures, both prevalence and levels of autoantibodies were much lower: only 2.0% detectable ANoA, and only 7.1% with detectable ANA. In the gold mining population, we also examined serum for AFA in those subjects with detectable ANoA (> or =1:10). There was no evidence for mercury induction of this autoantibody. CONCLUSIONS: This is the first study to report immunologic changes, indicative of autoimmune dysfunction in persons

exposed to mercury, which may also reflect interactions with infectious disease and other factors.

Lead differentially modifies cytokine production in vitro and in vivo.

Heo Y, Parsons PJ, Lawrence DA.

An imbalance between helper T cell type 1 (Th1) and helper T cell type 2 (Th2) activation can result in immunodysregulations leading to impaired cell-mediated immunity with an increased incidence of infectious disease or cancer and/or aberrant humoral immunity that may culminate with an autoimmune disease. Mercury, a heavy-metal toxicant, is known to induce renal autoimmunity characterized by a predominant Th2 response. Lead, another metal toxicant, causes enhanced B cell activities and impairs host resistance to several bacterial and viral infections. In addition, Pb was reported to enhance Th2 proliferation and inhibit Th1 proliferation. The differential effects of Pb on Th subset activation have been further investigated. In vitro IL-4 production by a Th2 clone was significantly increased by the addition of PbCl2, whereas IFN gamma production by a Th1 clone was decreased by the addition of PbCl2. When BALB/c mice were subcutaneously exposed to PbCl2, ex vivo Il-4 production by anti-CD3-stimulated splenic T cells was enhanced, but IFN gamma production was inhibited. Additionally, the plasma IL-4 and IgE levels of Pb-exposed mice were increased, and the plasma IFN gamma levels were significantly lowered in the absence of any additional exogenous antigen. In vitro, ex vivo, and in vivo treatment with HgCl2 produced similar findings. This study is the first report of the preferential activation of a Th2 response by Pb in vivo and suggests that PB, like Hg, may induce autoimmune responses by upsetting the balance between Th1- and Th2-like cells, which could enhance production of antibodies to self antigens.

Immunological effects of occupational exposure to metallic mercury in the population of T-cells and NK-cells.

Moszczyński P, Rutowski J, Słowiński S, Bem S.

This paper presents a study of the counts of lymphocytes, (CD3+)T-cells, (CD4+)T-helper and (CD8+)T-suppressor and (CD16+)NK-cells in the peripheral blood of 101 males with a history of occupational exposure to metallic mercury vapours (Hg0) and in 36 males without this exposure. These workers were divided depending on the duration of exposure: 37 males with a short-term history of exposure to Hg0 (up to 10 years) and 64 males with a history of long-term exposure (10 to 37 years). For the determination of T-cell populations monoclonal antibodies were used in indirect immunofluorescence tests. The time weighted average of mercury concentrations in air was 0.028 mg m-3. Mercury concentration in the urine of the exposed subjects ranged from 20-260 micrograms dm-3, and in blood it was from 4 to 72 micrograms dm-3. Stimulation of the T-cell line was noted as evidenced by increased numbers of (CD3+)T-cells, (CD4+)T-helper and (CD8+)T-suppressor cells in the workers with < 10 or > 10 years' exposure to Hg0. Lower increase count of (CD3+)T-cells and (CD4+)T-helper cells than (CD8+)T-suppressor cells was the cause of decreased values in the (CD3+)T/(CD8+)T-suppressor ratio and (CD4+)T-helper/(CD8+)T-suppressor ratio in the workers with < 10 or > 10 years' of exposure. Moreover, no changes were observed in the T-cell populations between workers with < 10 and those with > 10 years' exposure. In addition, statistical analysis of the effects of age and duration of exposure to Hg0 on the studied immunological parameters indicates that exposure duration may affect some of the values. These quantitative changes of T-cell population as well as changes of the (CD3+)T/(CD8+)T-

suppressor and (CD4+)T-helper/(CD8+)T-suppressor ratio have been proposed as immunological indicators of exposure to Hg0, which can be used for monitoring and to explain the origin of autoimmunity disorders induced by metallic mercury.

A study of autoantibodies and circulating immune complexes in mercury-exposed chloralkali workers.

Barregård L, Eneström S, Ljunghusen O, Wieslander J, Hultman P.

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.

Platinum-induced autoantibodies target nucleoplasmic antigens related to active transcription.

Chen M, Hemmerich P, von Mikecz A.

Research on autoimmune diseases has revealed that autoimmunity can be induced by heavy metals such as mercury and gold. Following the introduction of platinum-containing catalytic converters in automobiles, the emission of platinum compounds constitutes an abundant environmental pollutant, however, potential immunological hazards resulting from platinum-containing emissions were not yet examined. In our previous studies on molecular mechanisms of heavy metal-induced autoimmunity, we showed a platinum-dependent subcellular redistribution of the autoantigen fibrillarin from the nucleolus to the nucleoplasm. Since H-2s mice constitute a valuable model to study the role of heavy metals in the development of systemic autoimmunity, we treated susceptible B10.S mice with hexachloroplatinate (Na2PtCl6, Pt4+) to examine whether platinum induces the production of

autoantibodies. The present study shows for the first time that chronic administration of Pt4+ generated an autoimmune response in mice which targets distinct nucleoplasmic antigens. Dual-labeling revealed substantial colocalization of these nucleoplasmic autoantigens with (i) nascent RNA, (ii) the active, phosphorylated form of RNA polymerase II, and partial overlap with (iii) acetylated histone 4 protein, and (iv) 20S proteasomes in dendritic cells isolated from platinum-treated mice. The results suggest that platinum elicits antibodies against antigens associated with active sites of transcription which may be subject to proteasomal processing during heavy metal-induced autoimmunity.

Detection of mercury and other undetermined materials in skin biopsies of endemic pemphigus foliaceus.

Abréu Vélez AM, Warfvinge G, Herrera WL, Abréu Vélez CE, Montoya M F, Hardy DM, Bollag WB, Hashimoto K.

A novel variant of endemic pemphigus foliaceus (EPF) was described among individuals in an area surrounding El Bagre, Colombia, South America. The population in this rural mining community is exposed to high environmental levels of mercury, used for gold extraction, as well as other minerals, metalloids, and trace elements (e.g., quartz, rutile, granite, magnetite, and almenite) and ultraviolet radiation. Fifty control subjects and fifty EPF patients in the endemic area were examined for the presence of mercury in skin biopsies and hair, using autometallographic and mass spectroscopic analyses, respectively. Simultaneously, serum levels of IgE were measured, and cutaneous tests for hypersensitivity reactions were performed. Using autometallography, mercuric sulfides/selenides were detected in 14 of 51 skin biopsies distributed similarly in the control and patient groups. However, significantly higher serum IgE levels and mercury concentrations in hair, urine, and nails were found in patients compared with controls. Microscopic analysis revealed mercuric sulfides/selenides concentrated within and around the sweat gland epithelium, as well as in dendritic cells. Five skin biopsies from EPF patients and five from controls that tested positive for the presence of mercuric sulfides/selenides by autometallography were randomly selected for electron microscopic analysis. This analysis revealed a mixed electron-dense and electron-light material closely associated with desmosomes in patients. However, there were intracellular vesicles containing an amalgam of electron-dense and electron-light materials only in the EPF patients. Thus, EPF-affected individuals are exposed to high levels of environmental mercuric sulfides/selenides and other elements. This is the first study reporting mercuric sulfides/selenides in skin biopsies from people living in a focus of EPF, and these compounds may play a role in the pathogenesis of autoimmunity.

Occupational risk factors for the development of systemic lupus erythematosus.

Cooper GS, Parks CG, Treadwell EL, St Clair EW, Gilkeson GS, Dooley MA.

OBJECTIVE: There have been few studies of occupational exposures and systemic lupus erythematosus (SLE). We examined the association between the risk of SLE and occupational exposures (mercury, solvents, and pesticides), specific jobs (ever worked in teaching, healthcare, and cosmetology), and working night or rotating shifts. METHODS: Patients with recently diagnosed SLE (n = 265) were recruited through 4 university based and 30 community based rheumatology practices in North Carolina and South Carolina, USA. Controls (n = 355) were identified through driver's license records and were frequency matched to patients by age, sex, and state. Data collection included an in-person interview with detailed farming and work histories. RESULTS: Associations were seen with self-

reported occupational exposure to mercury (OR 3.6, 95% CI 1.3, 10.0), mixing pesticides for agricultural work (OR 7.4, 95% CI 1.4, 40.0), and among dental workers (OR 7.1, 95% CI 2.2, 23.4). Although these associations were fairly strong and statistically significant, the prevalence of these exposures was very low and thus these estimates are based on a small number of exposed cases and controls. Weaker associations were seen between SLE and shift work (OR 1.6, 95% CI 0.99, 2.7) and among healthcare workers with patient contact (OR 1.7, 95% CI 0.99, 2.9). There was no association of SLE with use of solvents or among teachers or cosmetologists. CONCLUSION: This study reveals the potential contribution of occupational exposures to the development of SLE, and highlights some exposures and experiences that should be examined in other studies using more extensive exposure assessment techniques and in experimental studies of autoimmunity.

Induction of autoimmunity through bystander effects. Lessons from immunological disorders induced by heavy metals.

Fournié GJ, Mas M, Cautain B, Savignac M, Subra JF, Pelletier L, Saoudi A, Lagrange D, Calise M, Druet P.

Autoreactive T cells exist in healthy individuals and represent a potential reservoir of pathogenic effectors which, when stimulated by microbial adjuvants, could trigger an autoimmune disease. Experimental studies have indicated that xenobiotics, well defined from a chemical point of view, could promote the differentiation of autoreactive T cells towards a pathogenic pathway. It is therefore theoretically possible that compounds present in vaccines such as thiomersal or aluminium hydroxyde can trigger autoimmune reactions through bystander effects.Mercury and gold in rodents can induce immunological disorders with autoimmune reactions. In vitro, both activate signal transduction pathways that result in the expression of cytokines, particularly of IL-4 and IFNgamma. In a suitable microenvironment heavy metals could therefore favour the activation of autoreactive T cells. In that respect, genetic background is of major importance. Genome-wide searches in the rat have shown that overlapping chromosomal regions control the immunological disorders induced by gold salt treatment, the development of experimental autoimmune encephalomyelitis and the CD45RC(high)/CD45RC(low)CD4(+)T cells balance. The identification and functional characterization of genes controlling these phenotypes may shed light on key regulatory mechanisms of immune responses. This should help to improve efficacy and safety of vaccines. Copyright 2001 Academic Press.

Murine metal-induced systemic autoimmunity: baseline and stimulated cytokine mRNA expression in genetically susceptible and resistant strains.

Häggqvist B, Hultman P.

Cytokines play an important and complex role in the pathogenesis of systemic autoimmune diseases. In susceptible H-2s mice, inorganic mercury (Hg) induces lymphoproliferation, antinucleolar antibodies against the 34-kDa-protein fibrillarin, and systemic immune-complex (IC) deposits. Here, we report extensive analysis of cytokine mRNA levels in susceptible A.SW (H-2s) and resistant A.TL (H-2tl) mice under unstimulated conditions and during oral treatment with Hg and/or silver nitrate (Ag). Cytokine mRNA expression in lymphoid tissues was assessed using the ribonuclease protection assay and phosphorimaging. Baseline expression of IL-2 and IFN-gamma mRNA was higher in A.SW than in A.TL mice. In A.SW mice, Hg treatment caused early up-regulation of IL-2 and IFN-gamma levels, followed by substantial expression of IL-4 mRNA, which was significant compared to control A.SW and

Hg-treated A.TL mice. Hg-exposed A.TL mice exhibited unchanged IFN-gamma, reduced IL-2 and greatly increased IL-10 mRNA expression. Ag-treated A.SW mice, which develop antifibrillarin antibodies (AFA) but exhibit minimal immune activation and no IC deposits, showed an early increase in IL-2 and IFN-gamma mRNA, but only a small and delayed rise in IL-4 mRNA. In conclusion, H-2-linked resistance to Hg-induced AFA is characterized by low constitutive expression of IL-2 and IFN-gamma mRNA, which is not increased by Hg, and a marked increase in IL-10 expression. Conversely, the key features of H-2-linked susceptibility to Hg- and Ag-induced AFA are up-regulation of IL-2, IFN-gamma and IL-4 mRNA expression, and down-regulation of IL-10 expression.

Reactions to metals in patients with chronic fatigue and autoimmune endocrinopathy]

Sterzl I, Hrdá P, Procházková J, Bártová J, Matucha P.

Our study was designed to assess the effect of heavy metals on the severity of fatigue in autoimmune thyroid disease associated with autoantibodies against other endocrine organs. We compared our data with those obtained from other groups of patients. A total of five groups of patients were examined by their medical history, dental examination, and using a modified test of blast transformation of metals (Melisa): a) 10 fatigues female patients with autoimmune thyroidism and polyglandular activation of autoimmunity, b) 12 fatigued patients with autoimmune thyroidism, c) 28 fatigued patients free of endocrinopathy, d) 22 professionals without evidence of autoimmunity, e) 13 controls, a population sample, the individuals did not complain of marked fatigue and their laboratory tests did not show signs of autoimmunity and endocrinopathy. Fatigue regardless of the underlying disease is primarily associated with hypersensitivity to inorganic and organic mercury, nickel, and gold. The groups differed in their hypersensitivity to other metals. In the control group, hypersensitivity--mostly to cadmium and lead--was found in four of the examined individuals only. Statistical analysis of data obtained from professionals and controls revealed a higher incidence of positivity to organic and inorganic mercury and nickel in professionals.

Report on health status of residents in areas with industrial, mining or military sites in Sardinia, Italy

Biggeri A, Lagazio C, Catelan D, Pirastu R, Casson F, Terracini B.

The work described in the present report has been requested by the Secretary of Hygiene, Health and Social Welfare of the Sardinia Region (Italy). It has been carried out by the Regional Epidemiological Observatory within the domain of ESA (Epidemiology Development and Environment) and with the support of the European Union. Eighteen areas (for a total of 73 municipalities) were identified a priori as "potentially polluted", accounting for a population of 917,977 in 2001 census (56% of the total population of Sardinia). The areas have been named after the most important town, as listed below (in brackets rounded 2001 population), major activities in industrial areas are briefly described. INDUSTRIAL AREAS: Portoscuso (59,000). Processing of aluminium and other metals. Foundry. Power plants. Dismissed mines (mainly coal mining, lead, zinc). Plants for storing and treating special wastes. Italian Law 349/1986 classified this area as "at high risk of environmental crisis" and classified some plants as being "at high technological risk" (Norma Seveso Decree 334/1999). The area is part of the Sulcis National Restoration site. San Gavino (24,000). Industrial and commercial activities. Lead and zinc foundry. Dairy factories. Food industry. Sarroch (52,000). Petrochemical and refinery industry. Power plants. Mining. Incinerator.

Plants for storing and treating special wastes. Gas and mineral oil deposits. Ottana (15,000). Chemical industry. Production of plastics and synthetic fibres. Denim production. Porto Torres (168,000). Chemical industry: production of basic chemicals (benzene, toluene, ethylene, propylene and others), polyethylene, elastomers and vinyl chloride. Textile industry. First and second category landfills. Some plants have been classified "at high technological risk" (Norma Seveso Decree 334/1999). The area is a National Restoration site. The town of Sassari is included. Tortolì (23,000). Construction of steel structures for offshore facilities of the oil and gas industry. Paper industry. Tempio Pausania (21,000). Cork production. Stone quarries. Macomer (17,000). Textile industry (velvet). First and second category landfills. Incinerator. MINING AREAS: Arbus (30,000). Extraction of zinc, lead and silver. Iglesias (39,000). Extraction of zinc, lead and silver. MILITARY SITES: Teulada (16,000). La Maddalena (11,000). Naval army shipyards. Salto di Quirra (31,000). Mining area. URBAN AREAS: Cagliari (299,000). Petrochemical plants, port, airport. Nuoro (37,000). Olbia (47,000). Port and airport. Oristano (31,000). Sassari (121,000). RESULTS: THE COMPARISON SARDINIA-ITALY: In 1997-2001, the age-standardized mortality rate (x1,000 person-years) among males was higher than in Italy (84.4 vs 80.8) while the reverse occurred in females (50.9 vs 52.0). Ill defined causes of death were 1.4% in males and 2.5% in females (vs corresponding estimates of 1.1% and 1.4% in Italy). Compared to Italian national data, regional age-standardized estimates were higher in Sardinia for infectious diseases (23% in males and 12% in females), respiratory diseases (22% and 14%: pneumoconiosis was more than 6 times more frequent in Sardinia than in Italy), diseases of the digestive system (26% and 9%: for liver cirrhosis, the excess was 33% in males and 9% in females; corresponding figures for liver cancer were 13% and 16%), breast cancer in females (5%). On the other hand, regional mortality rates were lower than the national rates for cardiovascular diseases (-1.3% and -7.4% in males and females respectively), all cancers considered as a whole (-9% and -7%) and lung cancer (-5% and -32%). Regional and national death rates for non Hodgkin lymphoma in both sexes and for leukaemia in females were almost identical, whereas the latter rate in males was slightly higher in Sardinia than in Italy (9.4 vs 8.4 x100,000 person-years). Particularly in men, the differences in mortality rates from all causes and from cardiovascular, respiratory diseases and lung cancer among the four traditional Provinces (Cagliari, Nuoro, Oristano and Sassari) were greater than the difference between Sardinia and Italy. Remarkably enough, also death rates from lymphohaemopoietic tumours were more heterogeneous within Sardinia. RESULTS IN THE INVESTIGATED AREAS: Rates of hospital discharges in Sardinia showed a high variability, which is partly attributable to differences in the availability of both hospital beds and alternative forms of care. This heterogeneity must be taken into account in the interpretation of rates of hospital discharge. These were relatively high in some areas (Cagliari, Iglesias, Portoscuso, Tortolì) and low in others (Olbia, Porto Torres, Sassari). All the reported observed/expected ratios were based on material deprivation adjusted figures. All the estimated statistics were reported with 90% Confidence Interval. INDUSTRIAL AREAS: In 1997-2001, deaths from respiratory diseases were significantly in excess in males in Portoscuso (obs/exp 205/124.77) and in San Gavino (69/46.77). Deaths from pneumoconiosis were recorded sporadically, with the exception of Portoscuso, where the excess was impressive (obs/exp 112/30.46). SMRs for lung cancer in males ranged between 0.62 in Ottana and 1.22 in San Gavino, with statistically significant departure from expected values in Portoscuso and Sarroch (both with SMR significantly in excess in males: 1.24). In Porto Torres mortality from all causes was in significant excess in both sexes (SMRs 1.04 in males and 1.09 in females), for respiratory diseases (1.08 and 1.28), for diseases of the digestive system (1.13 and 1.21), for all cancers (1.04 and 1.09). Liver cancer deaths were also in excess in both sexes (SMRs 1.18 and 1.21). The latter finding is confirmed by incidence rates from the local cancer registry. Among industrial areas, Porto Torres was also the one with a stronger evidence of an excess of deaths

from lymphohaemopoietic cancer in males (obs/exp 99/83.60) and females (73/68.20). MINING AREAS: These areas are characterized by statistically significant excesses of mortality in males, largely caused by non neoplastic respiratory conditions (obs/exp 119/86.41 in Iglesias and 156/62.55 in Arbus). In recent years, deaths from pneumoconiosis averaged 20 per year in Arbus and 10 per year in Iglesias. Lung cancer in males was also significantly in excess in both areas (obs/exp 72/56.38 in Arbus and 108/72.14 in Iglesias). There is a time trend (1981-2001) towards a decrease of mortality from respiratory conditions, which nevertheless remains largely in excess over the regional average also in the most recent period. MILITARY AREAS: Statistically significant excesses of deaths and hospital discharges for non Hodgkin lymphoma were detected in La Maddalena (mortality, 1981-2001, in males 17 observed cases vs 6.13 expected, in females 8/5.64). In Salto di Quirra in 1997-2001 deaths from myeloma (in males 5/2.3) and leukaemias were increased in both sexes (total obs/exp 20/13.3, statistically non significant). URBAN AREAS: Urban areas in Sardinia are relatively well developed with high values of socioeconomic indicators. The health profile in Cagliari and Sassari is typical of towns of the Western world. In Cagliari there is a higher mortality for colorectal, breast, cervical and lung cancer. CONCLUSIONS: Environmental (non occupational) pollution might explain some of the observed excesses of disease in the investigated industrial areas of Sardinia, particularly in women, less likely to be exposed to hazards in the work environment, whereas in the mining areas studied the disease pattern suggests a major role of occupational exposures. On the other hand, the causal links between disease occurrence and exposures in the screened military areas remain uncertain. The disease patterns in the cities of Sardinia are likely to be associated with lifestyle and urban pollution. Historically, southern Italian Regions have been characterized by an advantage over the rest of the country in terms of health, but during the last decade such advantage tended to vanish. Sardinia confirms this secular trend. However in the most recent years studied, overall age-standardized mortality rate in Sardinian females still remains lower than Italian average, but this is not the case for males any more. Differences in the health profile between residents in different areas of Sardinia have been found to be far greater than the difference between Sardinia as a whole and Italy. A major contribution to intraregional differences is given by the 18 investigated areas where excesses were registered for: respiratory diseases (including cancer) in the industrial areas of Portoscuso, Sarroch and Porto Torres, and in the mining areas; diseases of the digestive tract, liver cancer and lymphohaemopoietic cancer in the area of Porto Torres; cancer of the lymphohaemopoietic system in some military areas; cancers of the colon and rectum, lung, breast and uterus in some of the major cities of the Region.

Immune modulation by cadmium and lead in the acute reporter antigen-popliteal lymph node assay.

Carey JB, **Allshire A**, **van Pelt FN**.

Immune modulation by heavy metals may cause serious adverse health effects in humans, although the mechanisms involved are not well understood. Both cadmium and lead are important environmental and occupational toxins. Therefore, in the current study, the costimulatory/adjuvant effects and the T-cell-activating potential of these metals (i.e., CdCl2 and PbCl2), are examined. These immune-modulating properties are critical in the development of conditions such as allergy, hypersensitivity, and autoimmunity. Using the direct popliteal lymph node assay (PLNA) and reporter antigen-popliteal lymph node assay (RA-PLNA) both metals were examined individually for immunotoxicity. Mercury (i.e., HgCl2) was included for comparative purposes as its effects in the RA-PLNA are well documented. Seven days following a single footpad injection containing metal and/or RA

(trinitrophenyl-ovalbumin [TNP-OVA] or TNP-Ficoll), BALB/c mice were sacrificed and the popliteal lymph nodes (PLNs) removed. PLN cellularity, TNP-specific antibody-secreting cells (ASCs), and lymphocyte subsets were assessed. All three metals strongly stimulated T- and B-cell proliferation and ASC production following coinjection with the RA TNP-OVA. In each case, ASC production was skewed towards the IgG1 isotype. In addition, all three metals induced IgG production to TNP-Ficoll (although relatively weakly in the case of Cd). These results show that each of these metals can provide adjuvant signals to promote lymphocyte proliferation and enhance adaptive immune responses to unrelated antigens. Skewing of immune responses towards T helper type 2 responses suggests that each of these metals can enhance allergic and hypersensitivity reactions to environmental antigens. Furthermore, the induction of IgG responses to TNP-Ficoll, a T-cell-independent antigen, indicates that each of these metals can activate neoantigen-specific T cells. T-cell activation by metals can lead to metal hypersensitivity and has been implicated in the development of autoimmunity. This is the first report of immune modulation by CdCl2 and PbCl2 in the RA-PLNA.

Immunological disorders in men exposed to metallic mercury vapour. A review.

Moszczyński P.

The awareness of the effects of metallic mercury vapour on the human immune system has increased only in the last decade. The regulatory guidelines relating to testing for immunotoxicity of metals are not standardized so far. A full understanding of the relevance of the tests to man is still incomplete. Immunotoxicity investigation of metals in rodents, with subsequent extrapolation to man, forms the basis of human risk assessment. Human contact with mercury vapour is mainly in chloralkali plants and in factories producing controlling and measuring devices. When the immune system acts as a target of xenobiotic insults, the result can be a decreased resistance to infection, cancers, or immune disregulation that can induce the development of allergy, or autoimmunity (Fig. 1). This article reviews literature data and our studies concerning the immunotoxicity of metallic mercury vapour. A number of data shows that mercury exerts a suppressing effect but another data suggest stimulating effects on the human immune system. The results of immunological monitoring of individuals exposed to mercury vapour were either positive or negative as well as borderline and uncertain as to the influence of mercury vapour on human immune system. The positive data had no influence on the resistance of workers to infections and neoplasms. Skin and mucosa hypersensitivity to metallic mercury is rare. No positive report that mercury vapour could be carcinogenic in man has appeared up to now.

Silicium und Asbest:

Immunological Effects of Siliciea and Asbestos

Takemi Ptsuki, Meguni Maeda et al:

http://www.cmi.ustc.edu.cn/4/4/261.pdf

Herbicides and Insecticides

Acceleration of Autoimmunity by Organochlorine Pesticides in (NZB × NZW)F_1 Mice

Eric S. Sobel,[1] John Gianini,[1] Edward J. Butfiloski,[1] Byron P. Croker,[2,3] Joel Schiffenbauer,[1]* and Stephen M. Roberts[4]

http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=15743722

Prevalence of antinuclear antibodies in a rural population.

Rosenberg AM, **Semchuk KM**, **McDuffie HH**, **Ledingham DL**, **Cordeiro DM**, **Cessna AJ**, **Irvine DG**, **Senthilselvan A**, **Dosman JA**.

Exposure to environmentally and occupationally encountered toxicants can be associated with the development of certain autoimmune diseases and with the induction of antinuclear antibodies (ANA). Some chemicals used in the agricultural industry are known to affect immune function but their roles in the induction of autoimmunity in general, and ANA in particular, have not been reported previously. This study was undertaken to establish the prevalence of ANA in a rural population and to determine environmental and occupational exposures with which they are associated. This cross-sectional study represented one component of an interdisciplinary project (Prairie Ecosystem Study [PECOS], Eco-Research Program, Tri-Council Secretariat of Canada) designed to explore, in a rural population, the roles of environmental exposures as determinants of human health status. Information regarding lifetime, current, and main occupational exposures in the rural-dwelling study population was derived from a self-administered questionnaire. Sera from consenting subjects, collected during the months of February and March 1996, were assayed for ANA by indirect immunofluorescence on HEp-2 cells. The study population comprised 322 adult subjects (mean age 49.3+/-14.7 yr; range 16-87 yr). Statistical analyses adjusted for age and sex revealed that the presence of ANA among the participants was associated with a current agricultural occupation that included oilseed production, hog production, or poultry production. There was a significant association between ANA positivity and a current main farming operation of crop production. There was also an association among individual participants between lifetime exposure to the insecticide class of pesticides and the presence of ANA. In this rural study population, ANA positivity was significantly associated with lifetime exposure specifically to carbamate, organochlorine (including aldrin, chlordane, dieldrin, endrin, heptachlor, and lindane, but excluding DDT and methoxychlor), and pyrethroid insecticides and to phenoxyacetic acid herbicides, including 2,4-D. After adjustment for age, sex, and other insecticide exposures, multivariate analyses indicated that ANA positivity was associated with current oilseed production and with lifetime exposure to pyrethroid insecticides. In a rural population, ANA were associated with production of certain crops and certain animals and exposure to specific pesticides. The data indicate that some occupational exposures related to the agricultural industry are associated with the presence of ANA, a serologic expression of autoimmunity.

Acceleration of autoimmunity by organochlorine pesticides: a comparison of splenic B-cell effects of chlordecone and estradiol in (NZBxNZW)F1 mice.

Wang F, **Roberts SM**, **Butfiloski EJ**, **Morel L**, **Sobel ES**.

The weakly estrogenic organochlorine pesticide chlordecone can accelerate the development of systemic lupus erythematosus (SLE) in ovariectomized (NZBxNZW)F1 mice, with a shortened time to appearance of autoantibodies and disease similar to that produced by

treatment with the sex hormone 17beta-estradiol (E2). It is unclear whether chlordecone and E2 share the same pathways in mediating this effect. The effects of chlordecone and E2 treatment on splenic germinal center (GC) and marginal zone B cells were examined. Both chlordecone and E2 activated splenic B cells and enhanced GC reactions, as shown by upregulated protein expression of GL7, CXCR5, and CXCR4. Both treatments increased B-cell bcl-2 and shp-1 gene expression and enhanced ICAM-1 and VCAM-1 protein levels in GC B cells. Chlordecone reduced total B cell and GC B-cell apoptosis without affecting proliferation, another feature shared by E2 treatment. However, chlordecone treatment did not alter the composition of splenic B-cell subsets in marked contrast to the decrease in transitional B cells and increase in marginal zone B cells seen in E2-treated mice. The differences in effects between chlordecone and E2 indicate that chlordecone is not functioning simply as an estrogen mimic with respect to effects on the immune system. Similarities in the effects of chlordecone and E2 on specific immune functions, such as diminished apoptosis in GC B cells, may provide valuable clues regarding key events in the acceleration of autoimmunity by E2, chlordecone, and other agents.

Antinuclear antibodies and bromoxynil exposure in a rural sample.

Semchuk KM, **Rosenberg AM**, **McDuffie HH**, **Cessna AJ**, **Pahwa P**, **Irvine DG**.

Previous research suggests that farmers may have an increased risk of developing autoimmunity and that exposure to certain pesticides may alter immune function. Little is known, however, about the immunologic effects of farming and pesticide exposures. As part of the Prairie Ecosystem Study, associations between detection of antinuclear antibodies (ANA), an autoimmunity indicator, and exposure to the herbicide bromoxynil (3,5-dibromo-4-hydroxybenzonitrile) were investigated in a cross-sectional study of 208 residents (94 women, 114 men) of a cereal-producing region in Saskatchewan, Canada, during spring herbicide application, 1996. The ANA were assayed in serum by indirect immunofluorescence on HEp-2 cells. Bromoxynil was measured in plasma by gas chromatography/mass spectrometry analysis. Associations were explored between ANA detection and detection of bromoxynil in plasma, self-reported use of bromoxynil and other pesticides, farming exposures, gender, age, body mass index (BMI), and residency. The mean age (SD) of the participants was 50.8 (13.6) yr [women: 49.7 (13.5) yr, men: 51.6 (13.6) yr]. ANA prevalence was 37.5% (women: 39.4%, men: 36%,) at 1:40 serum dilution, 17.3% (women: 20.2%, men: 14.9%) at 1:80, and 10.1% (women: 13.8%, men: 7%) at 1:160. In the multiple-variable Generalized Estimating Equation (GEE) logistic regression analyses, female gender was a positive predictor of ANA detection and gender differences were observed in the relative importance of other study factors. None of the variables examined in the multiple-variable GEE analysis were statistically significant predictors of ANA detection for women. For many of these variables, however, the point estimates for women are similar to those seen in men. For men, with adjustment for age, ANA presence was inversely associated with detection of concentrations of bromoxynil in winter or spring samples and recent occupational use of 2,4-dichlorophenoxyacetic acid, and the positive ANA predictors included having a BMI in the obese (BMI > 30.04 kg/m2) category, recent occupational use of trifluralin or fungicides, and current exposure to oilseed, poultry, or dairy production. The inverse association between ANA detection and bromoxynil exposure observed in farmers in this study is consistent with earlier empirical observations that certain pesticides may suppress immune function. Further research is needed to examine whether these findings are confirmed in other populations and to elucidate the biological mechanisms involved.

Health of tree swallows (Tachycineta bicolor) nesting in pesticide-sprayed apple orchards in Ontario, Canada. I. Immunological parameters.

Bishop CA, Boermans HJ, Ng P, Campbell GD, Struger J.

The degree of pesticide exposure and its effects on the immune system and its development were determined in 16-d-old tree swallow (Tachycineta bicolor) chicks from 4 sprayed apple orchards and three nonsprayed sites in southern Ontario, Canada, during 1994-1995. Persistent contaminant residues were measured in tree swallow eggs and in each chick hepatic ethoxyresorufin O-deethylase (EROD) activity; body, immune organ, and liver masses; lymphocyte blastogenesis response; respiratory burst and phagocytic responses; hemarological evaluation; and histological development of thymus, bursa of fabricius, and spleen were determined. Chemicals sprayed on apple orchards were mainly ethylene bisdithiocarbamate and myclobutanil fungicides and organophosphorus, carbamate, and synthetic pyrethroid insecticides. During the period between oviposition of the first egg in each nest to d 16 after hatching, individual nests in orchards were exposed to between 4 and 11 individual chemical applications and up to 3 mixtures of pesticide sprays. Concentrations of pesticides, polychlorinated biphenyls (PCBs), and lead and arsenic residues in tree swallow eggs and liver were low and not variable among sites except p,p'-DDE, which was as high as 2.29 microg/g wet weight in eggs. EROD activity was not different among sites. Organochlorine and trace metal residues and EROD activity were not correlated with any immune parameter. In sprayed birds, we found a significantly increased blastogenic response to pokeweed mitogen (12.5 microg/ml). However, nests were initiated over a period of several weeks and we also found changes in other tree swallow immune parameters that were related to the date of chick collection. Hematological parameters, bursal and thymic masses, phagocytic response, and thymic development were all correlated with the day the chicks were 16 d of age. After accounting for the collection date of birds from each nest, we found cell proliferation in the cortex and delayed thymic involution correlated positively with increasing spray exposure. We also found that birds in sprayed orchards were slightly anemic compared to birds from nonsprayed sites, and there were smaller bursal masses and an increase in relative heterophil concentrations in the sprayed orchard birds. The local inflammation may have been caused by trematode parasite infections, although pesticide exposure also correlated positively with these parameters. This is the first study of the immunology and effects of current pesticide exposures in wild passerines; therefore it is difficult to predict the long-term consequences of the apparent stimulated immune systems in sprayed birds. However, some environmental contaminants that overtly stimulate the immune system in mammals have induced hypersensitivity and/or autoimmunity. Therefore we speculate that these effects are possible in tree swallows.

Differential effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin, bis(tri-n-butyltin) oxide and cyclosporine on thymus histophysiology.

De Waal EJ, Schuurman HJ, Van Loveren H, Vos JG.

Recent advances in the histophysiology of the normal thymus have revealed its complex architecture, showing distinct microenvironments at the light and electron microscopic level. The epithelium comprising the major component of the thymic stroma is not only involved in the positive selection of thymocytes, but also in their negative selection. Dendritic cells, however, are more efficient than epithelial cells in mediating negative selection. Thymocytes are dependent on the epithelium for normal development. Conversely, epithelial cells need the presence of thymocytes to maintain their integrity. The thymus rapidly responds to

immunotoxic injury. Both the thymocytes and the nonlymphoid compartment of the organ can be targets of exposure. Disturbance of positive and negative thymocyte selection may have a major impact on the immunological function of the thymus. Suppression of peripheral T-cell-dependent immunity as a consequence of thymus toxicity is primarily seen after perinatal exposure when the thymus is most active. Autoimmunity may be another manifestation of chemically mediated thymus toxicity. Although the regenerative capacity of thymus structure is remarkable, it remains to be clarified whether this also applies to thymus function. In-depth mechanistic studies on chemical-induced dysfunction of the thymus have been conducted with the environmental contaminants 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and bis(tri-n-butyltin)oxide (TBTO) as well as the pharmaceutical immunosuppressant cyclosporine (CsA). Each of these compounds exerts a differential effect on the morphology of the thymus, depending on the cellular targets for toxicity. TCDD and TBTO exposure results in cortical lymphodepletion, albeit by different mechanisms. An important feature of TCDD-mediated thymus toxicity is the disruption of epithelial cells in the cortex. TBTO primarily induces cortical thymocyte cell death. In contrast CsA administration results in major alterations in the medulla, the cortex remaining largely intact. Medullary epithelial cells and dendritic cells are particularly sensitive to CsA. The differential effects of these three immunotoxicants suggest unique susceptibilities of the various cell types and regions that make up the thymus.

Hexachlorobenzene

http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1566236&blobtype=pdf

Immunological consequences of exposure to pentachlorophenol.

McConnachie PR, **Zahalsky AC**.

Evaluation of lymphocyte phenotype frequencies, functional responses, serum immunoglobulin levels, and autoantibodies was completed for 38 individuals (i.e., 10 families) who were exposed to pentachlorophenol (PCP) in manufacturer-treated log houses. Comparison of subjects with controls revealed that the exposed individuals had activated T-cells, autoimmunity, functional immunosuppression, and B-cell dysregulation. Autoimmunity was evidenced by elevation of TA1 phenotype frequencies and a 21% incidence of anti-smooth muscle antibody. Functional immunosuppression was evidenced by the significantly reduced responses to all mitogens tested and to allogeneic lymphocytes in the mixed lymphocyte culture test. There was a significant elevation of CD10, and an 18% increase or decrease in serum immunoglobulins was noted. A striking anomaly was the enhanced natural killer activity found in exposed females but not in males.