Abstracted References Mercury and Neurological Disease

Mercury induced growth cone collapse: IN FOCUS NEURO REPORT 0959-4965 & Lippincott Williams & Wilkins Vol 12 No 4 26 March 2001 A23

Cases where exposure to heavy metals in the domestic and work environment have contributed to human disease extend back to antiquity with the use of lead in water pipes and wine storage vessels. It has been proposed that pandemic lead poisoning, resulting in mental incompetence and declining birth rate, especially amongst the ruling class, contributed to the fall of Rome [1] (see [2] for another view). More recent lead poisoning in the general population has arisen from lead-based paints and lead-additives in petrol. A well-documented case of occupational poisoning arose in workers of the 19th century felt hat industry due to the use of mercury as a stiffener of rabbit fur. Increased irritability, mood swings, tremulous- ness, ataxia and impairment in intellectual capacity characterize Mad Hatter's disease [3]. Currently there is ongoing public health debate on whether low level chronic exposure to mercury due to dental repair work results in subclinical behavioral changes associated with CNS damage (see [4] for review). For example, in the USA the most common material used in dental fillings is a mercury/silver mixture (amalgam) in which an estimated 70 000 kg is used in 100 million fillings/year. Furthermore, evidence indicates that mercury vapor is continuously released from tooth fillings where it is breathed in by the lungs and converted into mercuric ions. Although there is no debate on the toxic effects of high concentrations of mercury (i.e. associated with urinary concentrations .50 ìg/l), a challenge exists to demonstrate more subtle, preclinical effects associated with chronic low level mercury exposure in the general population with fillings. At least consistent with this notion is the study published in this issue [5] showing that exposure to mercury concentrations of ,0.1 ìM results in rapid (i.e. within 10 min) retraction of growth cones in snail neurons and is correlated with disruption of microtubules. Interestingly, the authors point out that similar disruption of microtubules is associated with Alzheimer's disease. These recent findings give added impetus for the development and implementation of alternative materials for fillings and may provide parents with added ammunition in teaching their children to floss.

Retrograde degeneration of neurite membrane structural integrity of nerve growth cones following in vitro exposure to mercury NeuroReport VOLUME: 12 ISSUE: 04 PAGES: 0733-0737 December 2000 Christopher C. W. Leong, Naweed I. Syed, Fritz L. Lorscheider

Inhalation of mercury vapor (Hg0) inhibits binding of GTP to rat brain tubulin, thereby inhibiting tubulin polymerization into microtubules. A similar molecular lesion has also been observed in 80% of brains from patients with Alzheimer disease (AD) compared to age-matched controls. However the precise site and mode of action of Hg ions remain illusive. Therefore, the present study examined whether Hg ions could affect membrane dynamics of neurite growth cone morphology and behavior. Since tubulin is a highly conserved cytoskeletal protein in both vertebrates and

invertebrates, we hypothesized that growth cones from animal species could be highly susceptible to Hg ions. To test this possibility, the identified, large Pedal A (PeA) neurons from the central ring ganglia of the snail Lymnaea stagnalis were cultured for 48 h in 2 ml brain conditioned medium (CM). Following neurite outgrowth, metal chloride solution (2 ml) of Hg, Al, Pb, Cd, or Mn (10–7 M) was pressure applied directly onto individual growth cones. Time-lapse images with inverted microscopy were acquired prior to, during, and after the metal ion exposure. We demonstrate that Hg ions markedly disrupted membrane structure and linear growth rates of imaged neurites in 77% of all nerve growth cones. When growth cones were stained with antibodies specific for both tubulin and actin, it was the tubulin/microtubule structure that disintegrated following Hg exposure. Moreover, some denuded neurites were also observed to form neurofibrillary aggregates. In contrast, growth cone exposure to other metal ions did not effect growth cone morphology, nor was their motility rate compromised. To determine the growth suppressive effects of Hg ions on neuronal sprouting, cells were cultured either in the presence or absence of Hg ions. We found that in the presence of Hg ions, neuronal somata failed to sprout, whereas other metalic ions did not effect growth patterns of cultured PeA cells. We conclude that this visual evidence and previous biochemical data strongly implicate Hg as a potential etiological factor in neurodegeneration.

The neuropsychiatric sequelae of mercury poisoning. The Mad Hatter's disease revisited. O'Carroll RE ; Masterton G ; Dougall N ; Ebmeier KP ; Goodwin GM ; Br J Psychiatry Vol. 167 no. 1 pp. 95-8 1995 Jul

Abstract
“The detailed effects of mercury poisoning on cognitive function, brain anatomy and regional brain function are largely unknown. We report the case of a 38-year-old man who was exposed to toxic levels of inorganic mercury.
“The patient developed a myriad of physical and psychiatric complaints, including stomatitis, muscle spasm, tremor, skin rash and the psychiatric syndrome known as 'erythism' (Mad Hatter's disease). Neuropsychological evaluation revealed marked and significant deficits of attention concentration, particularly when under time pressure. The MRI scan was unremarkable; however, SPECT revealed hypermetabolism of the posterior cingulate...”
“Mercury poisoning appeared to result in a dysregulation of posterior cingulate cortex, which was associated with attention/concentration deficits and marked anxiety/agitation.”
“Symptoms included attention/ concentration deficits, anxiety and agitation. This combined with the electrogalvanic effects previously mentioned, would also help explain the unusually rapid remission of neurological symptoms and signs in some patients following amalgam removal and which was unacceptable under the theory of chronic mercury toxicity. *It should not be forgotten that not only volatile solvents but even fresh water amoebae can gain access to the brain via the nose.”*

Comparison of Neurite Outgrowth with Neurofilament Protein Subunit Levels in Neuroblastoma Cells Following Mercuric Chloride Exposure. Abdulla, EM; Calaminici, M; Campbell, IC. Clin Exp Plnnarmacol Physiol., 22(5):362-3, May 1995.

ABSTRACT:
The objectives of the study were to establish that inhibition of neuronal differentiation in culture (assessed by neurite outgrowth) can be used as a broad spectrum in vitro measure of neurotoxicity.
To establish whether a rapid measure of neurite outgrowth could be used. Thus the study examined the relationship between the degree of neurite outgrowth assessed directly by image analysis and neurofilament protein subunit levels measured by ELISA.
SKNSH neuroblastoma cells, exposed for up to 6 days to mercuric chloride during initiation and continuation of differentiation, had lower levels of neurofilament proteins than unexposed cells.
Preliminary data from parallel examinations of neurite outgrowth assessed by image analysis and neurofilament protein subunit levels assessed by ELISA support a correlation when neurofilament protein levels are decreased by sub-cytotoxic doses of mercuric chloride in SKNSH cells.

Prenatal Coexposure to Metallic Mercury Vapour and Methylmercury Produce Interactive Behavioral Changes in Adult Rats. Fredriksson, A; Dencker, L; Archer, T; Danielsson, BR. NeurotoxicolTeratol, 18(2):129-34, 1996.

ABSTRACT: Pregnant rats were 1) administered methyl mercury (MeHg) by gavage, 2 mg/kg/day during days 6-9 of gestation, 2) exposed b~ inhalation to metallic mercury (Hg°) vapor (1.8 mg/m air for 1.5 h per day) during gestation days 14-19, 3) exposed to both MeHg by gavage and Hg° vapour by inhalation (MeHg + Hg°), or 4) were given combined vehicle administration for each of the two treatments (control). The inhalation regimen corresponded to an approximate dose of 0.1 mg Hg /kg/day.

Clinical observations and developmental markers up to weaning showed no differences between any of the groups. Testing of behavioral function was performed between 4 and 5 months of age and included spontaneous motor activity, spatial learning in a circular bath, and instrumental maze learning for food reward. Offspring of dams exposed to Hg° showed hyperactivity in the motor activity test chambers over all three parameters: locomotion, rearing and total activity; thio effect was potentiated in the animals of the MeHg + Hg
group. In the swim maze test, the MeHg + Hg° and Hg° groups evidenced longer latencies to reach a submerged platform, which they had learned to mount the day before, compared to either the control or MeHg group. In the modified, enclosed redial arm maze, both the MeHg + Hg and Hg° groups showed more ambulations and rearings in the activity test prior to the learning test. During the learning trial, the same groups (i.e., MeHg + Hg and Hg) showed longer latencies and made more errors in acquiring all eight pellets.

Generally, the results indicate that prenatal exposure to Hg° causes alterations to both spontaneous and learned behaviours, suggesting some deficit in adaptive functions. Coexposure to MeHg, which by itself did not alter these functions at the dose given in this study, served to significantly aggravate the change.
BID-PROBE COMMENT: This study is further evidence that prenatal exposure to mercury vapor is more harmful than prenatal exposure to methyl mercury, **which is** well acknowledged to be fetotoxic. Further, it should be noted that the damage is not evident from mere clinical observation. This study provides even more evidence that unborn babies should be protected from exposure to mercury from the amalgam fillings of their mothers.

Mercury vapor inhalation inhibits binding of GTP to tubulin in rat brain: similarity to a molecular lesion in Alzheimer diseased brain. Pendergrass JC, Haley BE, Vimy MJ, Winfield SA, Lorscheider FL Neurotoxicology 1997;18(2):315-324

Hg2+ interacts with brain tubulin and disassembles microtubules that maintain neurite structure. Since it is well known that Hg vapor (Hg0) is continuously released from "silver" amalgam tooth fillings and is absorbed into brain, rats were exposed to Hg 0 4h/day for 0, 2, 7, 14 and 28 d at 250 or 300 micrograms Hg/m3 air, concentrations present in mouth air of some humans with many amalgam fillings. Average rat brain Hg concentrations increased significantly (11-47 fold) with duration of Hg0 exposure. By 14 d Hg0 exposure, photoaffinity labelling on the beta-subunit of the tubulin dimer with [alpha 32P] 8N3 GTP in brain homogenates was decreased 41-74%, upon analysis of SDS-PAGE autoradiograms. The identical neurochemical lesion of similar or greater magnitude is evident in Alzheimer brain homogenates from approximately 80% of patients, when compared to human age-matched neurological controls. Total tubulin protein levels remained relatively unchanged between Hg0 exposed rat brains and controls, and between Alzheimer brains and controls. Since the rate of tubulin polymerization is dependent upon binding of GTP to tubulin dimers, we conclude that chronic inhalation of low-level Hg0 can inhibit polymerization of brain tubulin essential for formation of microtubules.

Metals and trace elements in plasma and cerebrospinal fluid in normal aging and Alzheimer's disease. Basun H, Forssell LG, Wetterberg L, Winblad B J Neural Transm Park Dis Dement Sect 1991;3(4):231-258

Cerebro-spinal fluid (CSF) and blood levels of aluminium, cadmium, calcium, copper, lead, magnesium, and mercury were studied in 24 subjects with dementia of the Alzheimer type (DAT) and in 28 healthy volunteers. Furthermore, arsenic, bromine, chrome, iron, manganese, nickel, rubidium, selenium, strontium, and zinc were measured only in blood. There were significant changes in the DAT group when compared to the controls. The plasma levels of aluminium, cadmium, mercury and selenium were increased and the contents of iron and manganese were lower in the DAT group as compared to control subjects. In CSF there were low levels of cadmium and calcium and increased content of copper in DAT cases. Iron and zinc levels in blood and calcium in both blood and CSF of DAT patients correlated with

memory and cognitive functions. Iron, manganese and strontium levels of DAT sufferers in blood and aluminium in CSF were related with changes in behaviour.

Long-term mercury excretion in urine after removal of amalgam fillings.Begerow J, Zander D, Freier I, Dunemann L Int Arch Occup Environ Health 1994;66(3):209-212

The long-term urinary mercury excretion was determined in 17 28- to 55-year-old persons before and at varying times (up to 14 months) after removal of all (4-24) dental amalgam fillings. Before removal the urinary mercury excretion correlated with the number of amalgam fillings. In the immediate post-removal phase (up to 6 days after removal) a mean increase of 30% was observed. Within 12 months the geometric mean of the mercury excretion was reduced by a factor of 5 from 1.44 micrograms/g (range: 0.57-4.38 micrograms/g) to 0.36 microgram/g (range: 0.13-0.88 microgram/g). After cessation of exposure to dental amalgam the mean half-life was 95 days. These results show that the release of mercury from dental amalgam contributes predominantly to the mercury exposure of non-occupationally exposed persons. The exposure from amalgam fillings thus exceeds the exposure from food, air and beverages. Within 12 months after removal of all amalgam fillings the participants showed substantially lower urinary mercury levels which were comparable to those found in subjects who have never had dental amalgam fillings. A relationship between the urinary mercury excretion and adverse effects was not found. Differences in the frequency of effects between the

Mercury concentration in the mouth mucosa of patietns with amalgam fillings. Willershausen-Zonnchen B, Zimmmerman M, Defregger A Schramel P Dtsch Med Ham G Wochenschr 1992 Nov 13;117(46):1743-1747

Mercury concentrations were measured in specimens of oral mucosa taken during oral surgery from 90 patients (53 men, 37 women, mean age 42 +/- 16 years); 30 of the patients had no amalgam fillings. All the mucosal specimens extended for at least 2-3 mm from the epithelium of the gingival margin and were clinically and radiologically normal. Thirteen patients without metallic fillings of any kind had mercury concentrations of 118.4 +/- 83.7 ng/g tissue, and in 17 patients with precious metal fillings but no amalgam the mean mercury concentrations were 144 +/- 290 ng/g tissue. Seventeen patients with 1-3 amalgam fillings had an average of 1975 +/- 4300 ng/g tissue and in 26 patients with 3-6 amalgam fillings the average concentration was 1158 +/- 2500 ng/g tissue. In 17 patients with more than six amalgam fillings the mean mercury concentration was 2302 +/- 5600 ng/g tissue. Although these results demonstrate a considerable degree of transfer of mercury from the amalgam fillings to the oral mucosa, it had not resulted in any clinically detectable mucosal lesions.

Quantitation of total mercury vapor released during dental procedures. Engle JH, Ferracane JL, Wichmann J, Okabe T Dent Mater 1992 May;8(3):176-180

An in vitro method is described in which measurements were made of the total amount of mercury vapor released from three types of amalgam during routine dental procedures. It was found that the greatest amount of mercury was released

during dry polishing of one amalgam (44 micrograms). Removal of amalgam from a Class I cavity under water spray and high volume evacuation also generated large amounts of mercury as expected (15-20 micrograms). However, under the more clinically relevant conditions of extending evacuation for one minute to remove residual amalgam and mercury after cutting, this value was reduced by approximately 90%. The total amount of mercury generated during placement (6-8 micrograms), wet polishing (2-4 micrograms) and trituration (1-2 micrograms) were also measured. The study showed that dental procedures associated with amalgam do potentially expose the patient and operator to mercury vapor. However, the total amount of mercury released during any procedure was far below the total exposure level calculated from the daily threshold limits established by regulatory agencies for occupational exposure.

The relationship between mercury from dental amalgam and mental health. Siblerud, Robert L, American Journal of Psychotherapy, Oct 1989 v43 n4 p575(13)

In the last century, hat makers who were exposed to mercuric nitrate often exhibited symptoms of mental illness, which included irritability, excitability, and shyness, earning them the name "Mad Hatters." Since that time, the relationship between mercury toxicity and health problems, both physical and mental, has been well documented. Dental amalgam, or "silver fillings," is used to fill 80 percent of the dental cavities in the world. This substance contains up to 50 percent mercury. Thus, it was hypothesized that there may be a relationship between dental fillings and mental health. It was also theorized that mercury in this form may enter the brain in cumulatively toxic levels through inhalation and by absorption into the cranial veins. One hundred one subjects were studied to determine the relationship between the presence of mercury amalgam fillings and mental health status. Half of the group had amalgam, while 51 had no fillings. The hair and urine of the subjects was monitored for the presence of mercury, and the subjects were given two questionnaires regarding levels of stress tolerance, physical health, and emotional or psychological symptoms such as anger or depression. Those in the amalgam group were found to have twice as much mercury in their urine and 26.5 percent more in their hair samples as the nonamalgam group. In addition, the subjects with fillings rated their reading comprehension significantly lower, and had significantly more episodes of sudden anger, depression, and irritability. In a separate, uncontrolled questionnaire given to dental patients who had their fillings removed, 67 percent claimed to have improved psychological status. Mercury has been related to stress, fatigue, premenstrual syndrome, and loss of short term memory. It is recommended that psychotherapists consider the possibility of mercury toxicity as a causative factor in disorders ranging from mild stress-related complaints to schizophrenia. (Consumer Summary produced by Reliance Medical Information, Inc.)

Moberg L.E. Corrosion products from dental alloys and effects of mercuric and cupric ions on a neuroeffector system. Swed Dent J [Suppl] 29:971-973, Aug 1985.

ABSTRACT: The release of corrosion products during long-term immersion in vitro of dental alloys, with particular reference to dissimilar alloys in contact

has been studied. The effects of Hg2+ and Cu2+ in low concentrations on the guinea-pig ileum have also been studied. The following conclusions were drawn: In an aggressive solution the release of elements from amalgams could be continuous and subsurface corrosion could cause a considerable increase in the corrosion products released. The change in microstructure observed in cross-sections of the corroded specimens was related to the amounts of corrosion products released into the saline solution. In an aggressive solution the corrosion products could increase when amalgams, Co-Cr, and Ni-Cr alloys are in contact with gold alloys, a high-Cu amalgam is in contact with a conventional amalgam, a type III gold alloy is in contact with gold alloys for metallo-ceramic purposes. The high-Cu amalgams released more corrosion products into the saline solution than a conventional one. Greater quantities of corrosion products were released from amalgams at pH 4 than at pH 6. Hg2+ and Cu2+ both had diverse and dose-dependent effects on the guinea-pig ileum. In low concentrations, 10nM, both ions exerted effects, probably on the muscle cell membrane.

Clarkson T.W. Metal toxicity in the central nervous system. Environ Health Perspect. 75:59-64,1987.

ABSTRACT: The nervous system is the principal target for a number of metals. Inorganic compounds of aluminium, arsenic, lead, lithium, manganese, mercury, and thallium are well known for their neurological and behavioral effects in humans. The alkyl derivatives of certain metals-- lead, mercury and tin--are specially neurotoxic. Concern over human exposure and in some cases, outbreaks of poisoning, have stimulated research into the toxic action of these metals. A number of interesting hypotheses have been proposed for the mechanism of lead toxicity on the nervous system. Lead is known to be a potent inhibitor of heme synthesis. A reduction in heme-containing enzymes could compromise energy metabolism. Lead may affect brain function by interference with neurotransmitters such as gamma-amino-isobutyric acid. There is mounting evidence that lead interferes with membrane transport and binding of calcium ions. Methylmercury produces focal damage to specific areas in the adult brain. One hypothesis proposes that certain cells are susceptible because they cannot repair the initial damage to the protein synthesis machinery. The developing nervous system is especially susceptible to damage by methyl- mercury. It has been discovered that microtubles are destroyed by this form of mercury and this effect may explain the inhibition of cell division and cell migration, processes that occur only in the developmental stages. These and other hypotheses will stimulate considerable experimental challenges in the future.

Nylander M., Friberg L., and Lind B. Mercury concentrations in the human brain and kidneys in relation to exposure from dental amalgam fillings.

ABSTRACT: Samples from the central nervous system (occipital lobe cortex, cerebellar cortex and ganglia semilunare) and kidney cortex were collected from autopsies and analyzed for total mercury content using neutron activation analyses.

Results from 34 individuals showed a statistically significant regression between the number of tooth surfaces containing amalgam and concentration of mercury in the occipital lobe cortex (mean 10. 9, range 2.4-28.7 ng Hg/g wet weight). The regression equation y = 7.2 + 0. 24x has a 95% confidence interval for the regression coefficient of 0.11-0. 37. In 9 cases with suspected alcohol abuse, mercury levels in the occipital lobe were, in most cases, somewhat lower than expected based on the regression line. The observations may be explained by an inhibition of oxidation of mercury vapor. The regression between amalgams and mercury levels remained after exclusion of these cases. The kidney cortex from 7 amalgam carriers (mean 433, range 48-~310 ng Hg/g wet weight) showed on average

Regional brain trace-element studies in Alzheimer's disease. Thompson CM Markesbery WR Ehmann WD Mao YX Vance DE Neurotoxicology (1988 Spring) 9(1):1-7

Alzheimer's disease (AD) brain trace-element imbalances in the amygdala, hippocampus and nucleus basalis of Meynert (nbM) are found in most cases to be consistent with those previously reported in samples derived principally from AD cerebral cortex (Ehmann et al., 1986). The elevation of mercury in AD nbM, as compared to age-matched controls, is the largest trace-element imbalance observed to date in AD brain. In addition to the general confirmation of imbalances for Cs, Hg, N, Na, P, and Rb noted previously in cerebral cortex samples, imbalances for Fe, K, Sc, and Zn were observed in two regions and one region also exhibited imbalances for both Co and Se. Persistent imbalances for the univalent cations Na, K, Rb and Cs support arguments for a membrane abnormality in AD. The data presented here also provide the first comprehensive simultaneous multi-element determinations in both control and AD nbM.

Mercury accumulation in tissues from dental staff and controls in relation to exposure**.** Nylander M Friberg L Eggleston D Bjorkman L Swed Dent J (1989) 13(6):235-43

Samples, mainly from occipital cortex and pituitary gland, but also from rental cortex, olfactory bulbs, thyroid gland and liver were collected from autopsies of 8 dental staff cases and 27 controls. These samples were analysed for total mercury content using radiochemical neutron activation analyses. The results revealed high mercury concentrations (median 815, range 135-4,040 micrograms Hg/kg wet weight) in pituitaries from the dental staff cases compared to controls (N = 23, median 23 range 6-1, 170 micrograms Hg/kg). In occipital cortex, the cases had a median of 17, range of 4-300 micrograms Hg/kg and the controls (N = 20) had a median of 10, range 2-29 micrograms Hg/kg. A few samples from olfactory bulbs show low mercury concentrations for both cases and controls. Renal cortex was analysed from three cases and contained clearly higher concentrations (945, 1,545, 2,110 micrograms Hg/kg) compared to controls (N = 12, median 180, range 21-810 micrograms Hg/kg). There is no control material for the other analysed samples, but one thyroid sample had an extremely high concentration of 28,000 micrograms Hg/kg.

Mercury concentrations in the human brain and kidneys in relation to exposure form dental amalgam fillings. Nylander m, Friberg l, Lind B, Swedish Dent J (1987) 11(5) :179-87

Samples from the central nervous system system (occipital lobe cortex, cerebellar cortex and ganglia semilunare) and kidney cortex were collected from autopsies and analysed for total mercury content using neutron activation analyses. Results from 34 individuals showed a statistically significant regression between the number of tooth surfaces containing amalgam and concentration of mercury in the occipital lobe cortex (mean 10.9, range 2.4-28.7 ng Hg/g wet weight). The regression equation y = 7.2 + 0.24x has a 95% confidence interval for the regression coefficient of 0.11-0.37. In 9 cases with suspected alcohol abuse mercury levels in the occipital lobe were, in most cases, somewhat lower than expected based on the regression line. The observations may be explained by an inhibition of oxidation of mercury vapour. The regression between amalgams and mercury levels remained after exclusion of these cases. The kidney cortex from 7 amalgam carriers (mean 433, range 48-810 ng Hg/g wet weight) showed on average a significantly higher mercury level than those of 5 amalgam-free individuals (mean 49, range 21-105 ng Hg/g wet weight). In 6 cases analysis of both inorganic and total mercury was carried out. A high proportion (mean 77% SD 17%) of inorganic mercury was found. It is concluded that the cause of the association between amalgam load and accumulation of mercury in tissues is the release of mercury vapour from amalgam fillings.

Could Mercury Fillings Influence Manic Depression? Journal of Orthomolecular Medicine (1998) 13:31

Amalgam fillings, which contain mercury, a potent neurotoxin, have become increasingly controversial in recent years. Most dentists insist that amalgam is safe, but a small group of self-styled "nontoxic" dentists claim that amalgam is harmful. A new study hints that amalgam fillings may play a role in bipolar disorder.

The researchers studied 20 men and women with manic depression. Eleven chose to have their amalgam fillings removed and replaced with ceramic fillings. The nine others opted to have either real or placebo plastic sealants placed over their fillings.

Before the study and eight months after the amalgam removal or sealant placement, the participants had their bipolar symptoms assessed using standard psychological tests. Compared with both sealant groups, the amalgam-removal group registered significant symptom improvement.

The researchers concluded that amalgam fillings may play a role in manic depression, and urged additional studies to clarify what is certain to be a controversial finding.

Cognitive Deficit in 7-Year-Old Children With Prenatal Exposure to Methylmercury." Grandjean, P; Weihe, P; White, RF; Debes, F; Araki, S; Yokoyama, I; Murata, K; Sorensen, N; Dahl, R; Jorgensen, PJ. Neurotoxicol Teratol., 19(6):417-28, Nov-Dec 1997.

ABSTRACT: A cohort of 1022 consecutive singleton births was generated during 1986-1987 in the Faroe Islands. Increased methyl mercury exposure from maternal consumption of pilot whale meat was indicated by mercury concentrations in cord blood and maternal hair.

At approximately 7 years of age, 917 of the children underwent detailed neurobehavioural examination. Neuropsychological tests included Finger Tapping; Hand-Eye Coordination; reaction time on a Continuous Performance Test; Wechsler Intelligence Scale for Children-Revised Digit Spans, Similarities, and Block Designs; Bender Visual Motor Gestalt Test; Boston Naming Test; and California Verbal Learning Test (children).

Clinical examination and neurophysiological testing did not reveal any clear cut mercury related abnormalities. However, mercury related neuropsychological dysfunctions were most pronounced in the domains of language, attention, and memory, and to a lesser extent in visuospatial and motor functions. These associations remained after adjustment for covariates and after exclusion of children with maternal hair mercury concentrations above 10 micrograms (50 nmol/g).

The effects on brain function associated with prenatal methyl mercury exposure therefore appear widespread, and early dysfunction is detectable at exposure levels currently considered safe.

Bio Probe COMMENT: This publication of the widely discussed Faroe Islands study should have dramatic impact on evaluation of mercury exposure to unborn babies. Obviously, the adverse effect is not detectable at birth, and shows a dramatic impact on quality of life for the affected individuals. It should be kept in mind that methyl mercury and mercury vapour are the two forms of mercury that readily penetrate cell membranes and accumulate in tissues of unborn babies. Methyl mercury is derived primarily from consumption of fish and seafood, whereas the primary contributor of mercury vapour to human body burdens comes from dental fillings.

Increased blood mercury levels in patients with Alzheimer's disease. Hock C, Drasch G, Golombowski S, Muller-Spahn F, Willershausen-Zonnchen B, Schwarz P, Hock, U, Growdon JH, Nitsch RM J Neural Transm 1998;105(1):59-68

Alzheimer's disease (AD) is a common neurodegenerative disorder that leads to dementia and death. In addition to several genetic parameters, various environmental factors may influence the risk of getting AD. In order to test whether blood levels of the heavy metal mercury are increased in AD, we measured blood mercury concentrations in AD patients (n = 33), and compared them to age-matched control patients with major depression (MD) (n = 45), as well as to an additional control group of patients with various non-psychiatric disorders (n = 65). Blood mercury levels were more

than two-fold higher in AD patients as compared to both control groups (p = 0.0005, and p = 0.0000, respectively). In early onset AD patients (n = 13), blood mercury levels were almost three-fold higher as compared to controls (p = 0.0002, and p = 0.0000, respectively). These increases were unrelated to the patients' dental status. Linear regression analysis of blood mercury concentrations and CSF levels of amyloid beta-peptide (A beta) revealed a significant correlation of these measures in AD patients (n = 15, r = 0.7440, p = 0.0015, Pearson type of correlation). These results demonstrate elevated blood levels of mercury in AD, and they suggest that this increase of mercury levels is associated with high CSF levels of A beta, whereas tau levels were unrelated. Possible explanations of increased blood mercury levels in AD include yet unidentified environmental sources or release from brain tissue with the advance in neuronal death.

Motor neuron uptake of low dose inorganic mercury. Pamphlett R Waley P J Neurol Sci (1996 Jan) 135(1):63-7

In animals, inorganic mercury can bypass the blood brain barrier and enter motor neurons. We sought to determine the lowest injected dose of mercury that could be detected in mouse motor neurons. Mice were injected intraperitoneally with mercuric chloride in doses from 0.05 to 2 micrograms/g body weight and studied between 5 days and 18 months after injection. After formalin fixation, 7 microns sections of cerebrum, cerebellum, brain stem, spinal cord and kidney were stained with silver nitrate autometallography. Five days after injection, mercury granules were detected at doses from 0.2 microgram/g upwards in the cell bodies of spinal and brain stem motor neurons, more granules being seen at the higher doses. Mercury granules were also seen in 5% of posterior root ganglion neurons. At doses from 0.05 microgram/g upwards mercury was detected 5 days later in renal tubule cells. Mercury was still present in motor neurons 6- 11 months after injection, but by this time mercury had been cleared from the kidneys. Low doses of inorganic mercury are therefore selectively taken up and retained by motor neurons, making this neurotoxin a good candidate for a cause of sporadic motor neuron disease.

Recovery from Amyotrophic Lateral Sclerosis and from Allergy after Removal of Dental Amalgam Fillings. Redhe, O; Pleva, J. J. Risk Safety Medicine. (1994): 4, 229-236.

An evaluation of 100 cases of poisoning and immunological effects in dental amalgam patients, documented in clinical practice. The patient had suffered for a long period from neurological problems. In 1984, following a complete neurologic evaluation, a diagnosis of amyotrophic lateral sclerosis (ALS) was made at the department of neurology of the University Hospital in Umea, Sweden. It is of unknown etiology and considered to be 100% fatal. No further visit to the clinic was proposed, as the disease is pernicious and there is no known therapy for ALS.

A dentist recognised the symptoms as those familiar in the patient group with health problems attributable to dental amalgam fillings. Patient history revealed the onset or

exacerbation of neurologic symptoms following placement of amalgam dental fillings. The patient had 34 tooth surfaces filled with amalgam, most of which were shallow and of moderate extent.

With the consent of the patient, all amalgams were removed and replaced with alternative material. Treatment was completed in March 1984. Removal of the amalgam in the first tooth that had originally given post-operative problems resulted in an exacerbation of symptoms, with a continued recurrence of exacerbation following each subsequent replacement.

Following the replacement of the last DA, the patient's entire condition rapidly improved. Six weeks following the final replacement, the patient was able to go up stairs without experiencing back pain. Pains in the mouth also receded and the sore throat, present during the whole history of the disorder, recovered. Five months after completion of the DA removal , the patient returned to the same University Hospital at Umea for a week- long follow-up investigation, after which the following notation was placed in her record: "The neurologic status is completely without comment . Hence, the patient does not show any motor neuron disease of type ALS. She has been informed that she is in neurological respect fully healthy."

Recovery from amyotrophic lateral sclerosis and from allergy after removal of dental amalgam fillings. Redhe O & Pleva J Int J Risk & Safety in Med 4:229-236 (1994)

CITATION FROM THE TEXT FOLLOWS:

"...Five months after the completion of DA removal (29 August 1984) the patient was called for a week-long investigation at the same University clinic where the diagnosis ALS had been made. She felt now extraordinarily healthy and her health status was also confirmed by the words in her record: "The neurologic status is completely without comment. Hence, the patient does not show any motor neuron disease of type ALS. She has been informed that she is in neurological respect fully healthy." ...At the time of writing (early 1993), 9 years have elapsed since removal of the DA fillings, and the patient continues to enjoy good health ... "

Metallothionein in ALS Motor Neurons. Kasarskis, EJ. FEDRIP Database, National Technical Information Service (NTIS).

ABSTRACT: Amyotrophic Lateral Sclerosis (ALS) is a chronic neurodegenerative disease, recognized clinically by its relentless progression of muscle atrophy, weakness, and eventual fatal outcome due to respiratory insufficiency. The illness has no effective treatment. The pathological hallmark of ALS is a selective death of motor neurons in the spinal cord and motor cortex. These features of ALS, however, fail to provide insight into its etiology with the result that several theories of etiopathogenesis have been advanced.

Our research focus is upon the potential involvement of toxic trace metals in causing the death of motor neurons. Heretofore, studies of toxic metals have only considered the possibility of excessive accumulation of a metal in the brain and spinal cord. Our work advanced the notion that mercury is present to excess in ALS patients when

compared to age-matched controls based on a multi-element analytical study using neutron activation analysis of several types of tissue. Further studies have suggested that mercury may be localized within spinal motor neurons using photoemulsion histochemistry. Thus it appears that mercury accumulates within the very cells which degenerate in ALS, suggesting that mercury may be a necessary precondition for ALS-type degeneration to occur.

OBJECTIVE: To investigate one aspect of mercury detoxification in ALS. As a prelude, we have ascertained the distribution of metallothionein (MT) in spinal cord by immunocytochemical methods using a polyclonal antibody to a defined epitope present in all forms of human MT. The Mts are a family of structurallysimilar, soluble, cysteine-rich, 6-7 kD proteins which detoxify heavy metals by sequestration and also regulate copper and zinc homeostasis.

In control subjects, we found MT immunoreactivity localized to the nucleus, cytoplasm, and axonal extensions of spinal motor neurons. In ALS spinal motor neurons, MT immunoreactivity was absent (or greatly reduced) in the nucleus. These findings open the possibility that abnormalities of MT may be involved in the pathogenesis of ALS. According to this formulation, MT may be structurally altered in ALS, greatly reduced in amount, or diverted from its normal nuclear localization as a result of toxic metal exposure.

PLAN and METHODS: The overall goal of this study is to isolate and sequence the Mts from the spinal cord of controls and compare the results to ALS patients to determine if Mts are altered in composition in ALS. The issue is a complicated one because: a) 6 MT isoforms have been sequenced from human tissues; b) 11 separate, but closely-related MT genes have been found; and c) MT has not been characterized from human spinal cord. To date, we have partially purified MT from bulk samples of control human spinal cord. Methods are in place to complete the purification of MT isoforms and determine their sequence.

After dissection of the anterior horn region and subcellular fractionation, we propose to isolate and identify the nuclear-associated MT isoform in control spinal cord. Strategies have been developed to deal with collateral issues such as the newly described MT-related protein, GIF. Guided by the results in controls, we will isolate the nuclear-associated MT(s) from ALS spinal cord. As a final test of the hypothesis, we will compare MT isoforms in motor cortex, the other region in which motor neuron degeneration occurs in ALS.

The results of these studies will evaluate the hypothesis that MT is altered in ALS . Finding an abnormality in MT would give considerable support to the concept tnat toxic metals are involved in the patnogenesis of ALS.

LOU GEHRIG'S DISEASE (ALS) THE MERCURY CONNECTION! BIOPROBE VOLUME 9 Issue 5 Sept. 1993

It cannot yet be said that mercury has been absolutely proven to be a causative factor in the development of ALS (Amyotrophic Lateral Sclerosis; " Lou Gehrig's Disease"); but recently published research definitely points to that probability.

As early as the mid 1950's, it had been established that the clinical features of chronic mercury intoxication at times mimic motor neuron disease. Subsequently, a number of case studies of ALS-like neuropathies caused by various forms of mercury have been documented.

Recent studies from the Departments of Neurology, Chemistry, Toxicology, Pathology and the Sanders-Brown Center on Aging of the University of Kentucky and the Veterans Administration Medical Center of Lexington, Kentucky further implicate mercury in the development of ALS. The following information is extracted from these studies. [It may be noted that some of the authors of these studies are recognizable as having published findings relating mercury to Alzheimer's Disease.]

Trace Element Imbalances In Amyotrophic Lateral Sclerosis Khare, SS; Ehmann, WD; Kasarskis, EJ; Markesbery, WR. Neurotoxicology. 11: 521-32. 1990.

ABSTRACT: Concentrations of 15 elements were determined by instrumental neutron activation analysis in brain, spinal cord, blood cells, serum and nails of Amyotrophic Lateral Sclerosis (ALS) patients and appropriately matched control subjects. Several significant imbalances were detected in trace element levels in ALS samples compared to control samples. Some of these changes are probably secondary to the loss of tissue mass, especially in spinal cord. However the widespread changes observed in Hg and se levels in ALS tissues deserve special attention. The significance of these alterations in trace element levels in relation to the pathogenesis of ALS is discussed.

The authors stated: "The changes observed in Hg concentration and the interactions of Hg and se are worthy of special comment and may possibly be relevant to the pathogenesis of ALS. Although an exact mechanism of Hg neurotoxicity has not yet been elucidated, Hg is known to have a high affinity for the sulfhydryl groups of proteins and may subsequently inactivate a protein or an enzyme. This could lead to total inhibition of the cellular function and to cell death."

BIO-PROBE COMMENT: The authors also discussed the significance of the selenium depletion, particularly in light of its established importance in the detoxification of mercury and protection against the adverse effects of mercury. This subject is discussed in detail in the following, more recent and comprehensive publication, which also addressed other important topics such as why ALS may develop in some individuals exposed to harmful agents (such as mercury) but not others.

Trace Metals In Human Neurodegenerative Diseases Kasarskis, EJ; Ehmann, WD; Markesberry, WR. Essential and Toxic Trace Elements in Human Health and Disease: An Update. Pg. 299-310. Wiley-Liss, Inc. 1993.

INTRODUCTION

Several examples of trace metal neurotoxicity causing recognizable classic syndromes have now been established. These have been documented resulting

from subacute or sustained chronic exposure to a toxic metal from an identified environmental source or by intentional poisoning.

Implicating toxic metals in the etiology or pathogenesis of chronic neurodegenerative diseases is more challenging for several reasons:

1. Dating the onset of the human neurodegenerative disease is uncertain, thereby making the identification of the source of exposure by epidemiologic study difficult. As a further complication of this factor, a significant degree of neuronal loss must occur before clinical dysfunction is apparent. In the case of ALS, it has been shown that 50% of spinal motor neurons will have degenerated before the typical features of the disease are noticed. Therefore, the exposure to a harmful neurotoxin could have occurred many years preceding the clinical onset of the disease.

2. Neurodegenerative disorders are caused by the death of select neurons, rather than wholesale destruction of tissue. The neurotoxin could therefore be very specific in its action and effective at a low dose, making systemic toxicity less likely.

3. Biopsy material is not usually available until post-mortem, which is at the end-stage of the disease. At this point, trace metal analysis of brain and spinal cord may not accurately reflect the biochemical condition when the disease process was set in motion.

THE PATHOLOGY OF ALS

Amyotrophic Lateral Sclerosis is a chronic neurodegenerative disease. It is characterized clinically by progressive atrophy and weakness of skeletal muscle and small local involuntary muscular contractions visible under the skin. Although clinical variants and familial forms of ALS occur, the classical disease is readily identified by physical findings and electrophysiological studies.

Pathologically, ALS is characterized by atrophy and degeneration of selective motor neurons in the ventral spinal cord and the motor cortex.

The etiology and pathogenesis of ALS are unknown. Viral inclusions have not been found, but study of the 5-10% of patients with a familial pattern suggest that a genetic defect may render motor neurons more susceptible to other secondary insults, such as exposure to an exogenous toxin.

THE INVOLVEMENT OF TOXIC METALS IN ALS

The toxic trace element theory of the pathogenesis of ALS has received considerable support and derives its attractiveness from three sources:

1. Epidemiologic considerations indicate that long-term exposure to heavy metal is more common among ALS patients compared to controls.

2. An ALS-like syndrome has been linked to chronic intoxication with mercury and lead.

3. Environmental factors have been implicated in the etiology of a related motor neuron disorder; ie, ALS/Parkinson' s/Dementia in Guamanian subjects.

To date, most studies have examined a very basic hypothesis, that ALS may be caused by chronic, low-level exposure to toxic metals. If this hypothesis is true, then one should be able to analyze tissue from ALS patients and demonstrate that the concentration of toxic metals is higher in ALS compared to age-matched controls.

RESULTS

We began our studies of ALS in this traditional mode by analyzing several tissues (brain, spinal cord, serum, blood cells, and nails) from patients and controls for 15 elements by instrumental neutron activation analysis (INAA). The most important finding was a significant elevation of mercury in brain, blood cells, and serum in ALS patients compared to age- matched controls. The elevation of mercury in ALS could reflect a true excess of body burden of mercury, altered turnover, or perhaps binding to unusual intracellular ligands.

The results of our study also indicated that selenium was reduced in the serum and blood cells of ALS patients. The data were more striking when the ratio of mercury:selenium was computed for each sample in order to study both elements concurrently. This approach not only considered the accumulation of a toxic metal, but also evaluated the integrity of potential detoxification mechanisms. The results of our work indicated that mercury was present to excess relative to selenium in ALS blood cells, serum, and brain.

We have considered that mercury accumulation in motor neurons may be a necessary precondition for ALS-type degeneration to occur. This hypothesis predicts that mercury should be enriched in spinal motor neurons of normal spinal cords and that additional factors would impinge on motor neurons to cause their degeneration in ALS. Our formulation is specific in proposing:

Mercury accumulation by neurons is a prerequisite for subsequent neurodegenerative changes to ensue.

2. The ALS phenotype develops either by excessive mercury accumulation or inadequate mercury detoxification.

If mercury is, in fact, an etiologic factor in the pathogenesis of ALS, then one would predict the mercury would accumulate in precisely those neurons which ultimately degenerate in ALS. In order to evaluate this hypothesis, the analysis of mercury must be investigated on a cell-by- cell basis.

Because LAMMS (Laser-Activated Microprobe Mass Analysis) did not provide the requisite sensitivity to detect mercury under our conditions, the mercury-specific photoemulsion histochemical (PH) method described by Moller-Madsen and Danscher in 1986 was adapted to human postmortem spinal cord. Mercury was found localized primarily to the nucleus of motor neurons with lesser amounts seen in the cytoplasm. Mercury was also found associated with spinal motor neurons in normal humans. These data, together with the results of the buLk tissue analyses,

indicate that spinal motor neurons have an avidity [ED: Strong affinity] for mercury which could possible render them more susceptible to other neurotoxic agents, thereby conferring a selective vulnerability to neuronal degeneration.

Metallothionein in als: some speculations and direction for future research.

Metal detoxification may be the more critical factor in the pathogenesis of ALS because it appears unlikely that ALS results from a simple, environmental-type exposure based upon population studies.

The metallothionein (MT) family of proteins has not been investigated in ALS. The rationale for studying MT in ALS receives support from the detailed understanding of MT from human and animal studies.

Our preliminary data implies that at least part of the accumulated mercury may be bound to MT in motor neurons. It is premature to seriously speculate on potential mechanisms, although MT could directly detoxify mercury. Alternatively, mercury could conceivably divert MT from its function in copper and zinc homeostasis.

Our findings suggest a potential mechanism to explain the selective death of spinal motor neurons in ALS, namely an imbalance between mercury accumulation and detoxification of mercury. Our hypothesis considers that inadequate mercury detoxification by MT might occur in ALS spinal and cortical motor neurons leading to neuronal death. Impaired detoxification could result from an aberrant MT isoform within spinal motor neurons or altered MT gene expression following mercury exposure.

BIO-PROBE COMMENT: This presentation is dramatic and compelling. The credentials of the investigators, institutions, and publications are impressive. The techniques, investigative protocols and rationale are beyond reproach.

It should be obvious to even the most biased, that continued acceptance of doctrines and rationales that permit human chronic low-level exposure to mercury, are totally without scientific support, and cannot be condoned any longer.

Kasarskis, EJ. Metallothionein in ALS Motor Neurons. FEDRIP Database, National Technical Information Service (NTIS).

ABSTRACT: Amyotrophic Lateral Sclerosis (ALS) is a chronic neurodegenerative disease, recognized clinically by its relentless progression of muscle atrophy, weakness, and eventual fatal outcome due to respiratory insufficiency. The illness has no effective treatment. The pathological hallmark of ALS is a selective death of motor neurons in the spinal cord and motor cortex. These features of ALS, however, fail to provide insight into its etiology with the result that several theories of etiopathogenesis have been advanced.
Our research focus is upon the potential involvement of toxic trace metals in causing the death of motor neurons. Heretofore, studies of toxic metals have only considered the possibility of excessive accumulation of a metal in the brain and spinal cord. Our work advanced the notion that mercury is present to excess in ALS patients when compared to age-matched controls based on a multi-element analytical study using

neutron activation analysis of several types of tissue. Further studies have suggested that mercury may be localized within spinal motor neurons using photoemulsion histochemistry. Thus it appears that mercury accumulates within the very cells which degenerate in ALS, suggesting that mercury may be a necessary precondition for ALS-type degeneration to occur.

Inorganic mercury is transported from muscular nerve terminals to spinal and brainstem motoneurons. Arvidson B. Muscle Nerve. 15(10):1089-1094, Oct 1992.

ABSTRACT: The distribution of mercury within the brainstem and spinal cord of mice was investigated with the autometallographic technique after intramuscular administration of a single dose of mercuric mercury (HgCl2). Deposits of mercury were localized to motor neurons of the spinal cord and to brainstem motor nuclei; i.e., neurons with their peripheral projections outside the blood-brain barrier. Unilateral ligation of the hypoglossal nerve prior to the injection of HgCl2 prevented the accumulation of mercury deposits in the ipsilateral hypoglossal nucleus. The selective accumulation of mercury in spinal and brainstem motoneurons is most probably due to a leakage of metal-protein complexes from capillaries in muscle into myoneural junctions, followed by uptake into nerve terminals and retrograde axonal transport. The possible link between this process and the development of motor neuron degeneration in ALS is discussed.

BIO-PROBE COMMENT: It is time that the medical profession took cognizance of the fact that some Amyotrophic lateral sclerosis (ALS) patients improve or become symptom free after amalgam replacement. Animal and human research studies are providing the scientific basis and support to ALS patient case histories reflecting amelioration or cure of this "incurable" disease.

Motor Neuron Uptake of Low Dose Inorganic Mercury. Pamphlett, R; Waley, P.J Neurological Sciences, 135:63-7,1996.

ABSTRACT: In animals, inorganic mercury can bypass the blood brain barrier and enter motor neurons. We sought to determine the lowest injected dose of mercury that could be detected in mouse motor neurons. Mice were injected intraperitoneally with mercuric chloride in doses from 0.05 micrograms/g body weight and studied between 5 days and 18 months after injection. After formalin fixation, 7 micrometer sections of cerebrum, cerebellum, brain stem, spinal cord and kidney were stained with silver nitrate autometallography. Five days after injection, mercury granules were detected at doses from 0.2 micrograms/gram upwards in the cell bodies of spinal and brain stem motor neurons, more granules being seen at the higher doses. Mercury granules were also seen in 5 % of posterior root ganglion neurons. At doses from 0.05 micrograms/gram upwards mercury was detected 5 days later in renal tubule cells. Mercury was still present in motor neurons 6-11 months after injection, but by this time mercury had been cleared from kidneys. Low doses of inorganic mercury are therfore selectivel taken up and retained by motor neurons, making this nurotoxin a good candidate for cause of sporadic motor neuron disease.

BIO-PROBE COMMENT: This new study should be of great interest to scientists who have already connected exposure to mercury to motorneuron diseases such as

Amyotrophic Lateral Sclerosis (Lou Gehrig's Disease). Previous research, dating back to the 1960's, has demonstrated that inorganic mercury (Hg 2+ does penetrate the blood-brain barrier, but at a low rate. Mercury vapor, the form released from dental amalgam fillings penetrates the blood-brain barrier far more readilly. We must also consider that the above findings represent findings from just a single dose, whereas patients with amalgam fillings receive thousands of doses of mercury vapour every day.

Toxicity of Ionic Mercury and Elemental Mercury Vapour on Brain Neuronal Protein Metabolism. Lorscheider, FL; Vimy, MJ; Pendergrass, JC; Haley, BE.

ABSTRACT: Numerous reports establish that amalgam mercury (Hg) vapour is continuously released from tooth fillings into mouth air, and for the general population this form of Hg exposure is greater than all other environmental sources combined. Uptake and accumulation of amalgam Hg occurs in various monkey and human tissues, including brain (Goering et al., Fundam Appl Toxicol., 19:319-329, 1992). Our laboratories now focus on the effects of inorganic Hg (both ionic and vapor forms) upon CNS neuron function.
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Baginski B. Effect of mercuric chloride on microbicidal activities of human polymorphonuclear leukocytes. 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.
BIO-PROBE COMMENT: Two more studies demonstrating the potentially devastating effects on the immune defense systems that can be caused by exposure to mercury. Hopefully, the chapter on the predicted intake of mercury vapor from dental amalgams included in the February 1988 edition of "The Biological Monitoring of Toxic Metals" published by Plenum Press will begin to alert the medical profession to the necessity of considering mercury toxicity as a possible etiological factor when working with immune-incompetent patients.