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OCCUPATIONAL INTOXICATION OF MERCURY

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Mercury (Hg) is a metal, and a natural component of the ocean and earth's crust. Compared to other elements, Hg is not a major component of the biosphere. The weather and human industry release Hg into the air and water, resulting in its redistribution and increasing the risk of human exposure. Everyone is exposed to Hg at some level, but any avoidable exposure to Hg is undesirable because Hg is not essential to any bodily functions. When Hg becomes concentrated in the air, water, or foods as a result of human activity, it is considered to be a pollutant. Modern techniques can detect Hg in parts per billion (ppb) concentrations in the air or water (see Indices of Exposure, below). Mankind has used mercury since history began, most recently as a germicide and preservative, (e.g., in eye drops), for production of paper pulp, in chemical processes such as alkaline-chlorine plants, and in the manufacturing of vinyl. Hg is released from burning of fossil fuels and waste materials. Monitoring of environmental contamination may employ chemical analyses of sentinel animals or plant species that accumulate Hg from air or water, as well as specimens taken directly from humans. These monitoring strategies are discussed below.

Mercury exists in three forms: elemental (a liquid commonly known as quicksilver), inorganic mercury compounds, and organic compounds. Although all forms of Hg are toxic, the specific form of Hg influences how Hg moves through the environment and within the body. Both elemental and organic mercury are volatile and absorption by inhalation is significant. The GI tract accounts for the most significant absorption of inorganic Hg salts, and for nonoccupational exposures to organic Hg via the ingestion of foods.

The toxicity of Hg compounds is the result of their affinity for sulfur and sulfhydryl groups; this affinity facilitates Hg binding with proteins, which in turn results in cytotoxicity. Alkylmercurials, the most toxic form of Hg, have a high absorbance from the GI tract and a slow rate of elimination from the body. These properties cause alkylmercurials to accumulate in both soft and hard tissue with continued exposure, even if the daily exposure is rather low. Details of the uptake, binding, distribution, and metabolism of Hg have been well described.

Epidemiology. Occupational exposure represents a significant portion of Hg poisoning cases. Miners extracting gold from Hg, or extracting Hg ore (mercuric sulfide, cinnabar, is the most prevalent form) provided early cases of occupational poisoning. Exposure is mostly by inhalation. Respiratory problems dominate the effects of short-term inhalation exposures. Longer-term exposures bring on signs of nervous system disorders (see Indices of Effects, below). Miners may have neurobehavioral deficits that persist for more than 10 years after the end of exposure.

The dental profession conveys higher risk of Hg poisoning because mercury-silver amalgams have been extensively used to fill dental caries. Exposure is by inhalation and dermal routes. Procedures for handling Hg in dentistry have improved along with increasing awareness of the health hazards of low-level exposure to Hg, and Hg amalgams are now used in only half of the dental restorations of Americans. Dental personnel may have higher levels of Hg in their bodies and may have higher incidence of nervous system impairment than employees of similar socioeconomic status who do not work with Hg. Female dental assistants whose work involved substantial use of Hg amalgams and who

practiced "poor mercury hygiene" were less fertile than others who used less Hg in their work. Oddly, the women who used small amounts of amalgam in their work were more fertile than the control group who worked in dental offices that did not use amalgams. These results illustrate that more research is needed before we can fully understand the effects of low-level exposure to Hg.

Hg is also used in the calibration of glass, in fluorescent lamps, and in thermometers and electrical switches. Workers who had used elemental Hg to calibrate glassware illustrate the onset and recovery from Hg-induced tremor. Other current industrial uses are in paper pulp processing and in alkaline-chlorine factories. Clinical descriptions of these and other categories of occupational Hg poisoning of historical interest were described in the classic reference Hunter's Diseases of Occupations.

Mercury in the Food Chain. Ingestion of Hg in food is responsible for the largest number of nonoccupational exposures. Hg is taken up by terrestrial and aquatic plants, which become food for humans and other animals. Inorganic Hg is converted to the more toxic organomercurial compounds, primarily by methylation by anaerobic microorganisms in the sedimentary layers of seas and lakes. As larger animal species feed on the plants or smaller animals, the content of Hg in the tissues becomes concentrated, reaching its highest levels in large fish such as tuna, and other predators at the top of the food chain. The major portion of Hg in fish is methylmercury. The risk from heavy consumption of these fish has caused public authorities to regulate the marketing of seafood having >1 part per million (ppm) Hg. Some seafoods contain significant amounts of selenium. Experiments indicate that selenium binds some of the Hg and thus reduces the toxicity that would occur with a given concentration of Hg without selenium.

The most profound examples of people poisoned by environmental Hg were in Iraq, where thousands of people were poisoned after making bread from seed grain that had been treated with methylmercury as a fungicide and in Minamata, Japan. The Japanese episode illustrated the conversion of inorganic Hg to the more toxic organic forms, by aquatic organisms. Hg was discharged from a factory that used mercuric chloride in the manufacture of vinyl chloride. The effluent from the factory drained into a bay. Seafood was a principal part of the diet of the local people. The complex path of the runoff of inorganic Hg pollution from land to sea, its conversion to the highly toxic methylmercury, accumulation in the food chain, and finally the delayed manifestations of neurotoxicity among people made it difficult to trace the cause. The tragedies in Iraq and Japan also illustrated the fetus's higher vulnerability to Hg, with the most severe cases becoming apparent at birth but others displaying more subtle deficits later in the developmental process.

Attention has now shifted to children of fish-eating populations. Residents on islands (Seychelles, Faroes) where sea fish are the main component of the diet have slightly higher concentrations of Hg in their blood and hair than do other populations. These studies showed that mothers can transmit Hg to their fetus through their blood supply, and to their infant through maternal milk. Clear evidence of toxic effects is being sought for these relatively low exposures.

Mercury Exposure from Dental Amalgams. Metallic Hg accounts for about 50% of the material in most dental fillings, and small amounts of Hg vapor are released from fillings. The World Health Organization recently concluded that Hg-silver amalgams, used in dentistry for about 150 years, offer several advantages over alternative materials for dental restorations; they provide a desirably hard surface, and are inexpensive and long-lasting. Most dentists believe that amalgams present the patient with no more health risk than that associated with alternative materials. However, people with Hg amalgams exhale increased levels of Hg after brushing teeth or chewing gum and have higher levels of Hg in their blood or maternal milk than persons with few fillings. Hg from amalgams may be absorbed into the body through the buccal mucosa, the lung or the digestive tract. Hg appears in the nervous system and kidney of laboratory animals after they were given dental amalgams. These data demonstrate the uptake of Hg from amalgams into the body,

but do not indicate whether the amount of Hg absorbed from amalgams contributes to health impairment.

Long-term exposure to Hg from dental amalgams can be quantified by the number of amalgam surfaces in the mouth. The level of Hg in the urine represents primarily recent exposure, but urinary Hg levels may be proportional to the number of amalgams. Hg content of the blood and urine of adults with amalgam restorations is quite low, but Hg is known to accumulate in the kidney and nervous system, where it is less easily measured. Thus, there has been considerable speculation that accumulated Hg from dental amalgams may contribute to health problems (see Questions about Chelation Therapies, below).

There is little solid evidence of deleterious health effects that can be traced unambiguously to amalgam. The largest body of research on health effects of amalgams has been done in Sweden. Large epidemiologic studies of adults found no significant impairment of renal or immune systems related to amalgams. One study reported no relationship between amalgams and children's allergic problems. However, there is sufficient concern about Hg from amalgams affecting the more vulnerable, juvenile population to cause the National Institute of Dental Research to begin prospective clinical trials, the strongest experimental design for identifying health hazards from amalgams. At present, the large-scale replacement of an individual's amalgam fillings with nonmetallic materials seems unjustified because the drilling releases Hg and thus worsens the patient's exposure. Occult religions and alternative medical practices lead to some Hg poisonings. Santeria, a quasi-religious practice that has been transplanted from the Caribbean islands, employs elemental Hg in potions that are thought capable of banishing evil forces from a person or their home. It is not surprising that exuberant use of such potions may result in accidental poisoning, but the extent of poisoning attributable to folk remedies is not known.

Pathophysiology. The metabolism of Hg compounds has been reviewed by Goyer. The molecular mechanisms of Hg toxicity have been reviewed in terms of "molecular mimicry," in which the methylmercury cation reacts with the amino acid cysteine to form a compound that mimics the amino acid methionine and thus gains entry into the cell on the amino acid carrier. Toxicity results when Hg does not mimic essential ions and molecules in every circumstance. Additional molecular mechanisms have been reviewed by Atchison and Spitsbergen. Many reports have demonstrated that Hg compounds, particularly methylmercury, damage neurons. A current question is whether the effects of Hg can be more clearly understood with reference to the role of glial cells in the brain's defense and the repair processes. Two type ofglia, microglia and astroglia, may serve as filters, defending against of metals entering the brain. Glia also contribute to the repair of damaged neurons. The astroglial cells are affected in early stages of Hg neurotoxicity. However, the question is whether the defense and repair processes may, in some cases, occur at the expense of surviving cellular processes, and thus worsen rather than restore Hg-induced impairment.

INDICES OF EXPOSURE. Air, Water, and Industrial Hygiene Control

Exposures to Hg in the workplace have become lower, and fewer cases of Hg poisoning are reported after governmental regulation of many organo-Hg compounds. Exposure to Hg in the ambient air can be documented with personal monitoring devices.

Indices of human body burden are obtained by Hg content of hair, blood, and urine. Most cases of Hg toxicity are associated with detectable Hg in the urine. Exposure to metallic Hg vapor and inorganic Hg can be monitored in urinary Hg concentration, after adjustment for creatinine content. Concern should be triggered by biologic exposure Hg index values of>35 lg/g creatinine in urine. Exposure to methyl Hg is best indicated by the concentration of Hg in whole blood, where it is sequestered in the red cells. Blood Hg concentration is a better index of recent exposure to methylmercury than is urinary Hg. The elimination of Hg from blood and urine is much more rapid than from the whole body. Thus, blood and urine Hg concentrations are most influenced by recent exposures (e.g., within a week) and provide less evidence of past exposures.

A more extended chronology of past exposure to methyl Hg can be determined from the analysis of the concentration gradient of Hg along a strand of hair. Analysis of Hg

in maternal hair may provide good evidence of fetal exposure during the various gestational stages. Hair and fingernails are useful indicator media for two reasons: these tissues are composed mostly of keratin, a protein that is formed from many sulfhydryl groups that can bind Hg during the growth process, and because cells of hair and nails survive for a relatively long time. However, care is required to avoid contamination of hair and nails with Hg external to the body, e.g., in dusts and cosmetic products.

Biologic specimens can be analyzed for total Hg content by atomic absorption methods. Cold vapor atomic absorption spectrometry is the most commonly used method to measure Hg in biologic samples. Digestion of the specimen may be required to liberate ionic Hg from the chemical matrix in which Hg is bound. Total mercury may be further analyzed into its organic and inorganic components, if gas chromatography is combined with the atomic absorption method. Other methods and their suitability, depending on the expected concentration of Hg in the specimen and the matrix in which Hg has been found, have been reviewed frequently.

Biomarkers

Many new methods are being assessed for their ability to detect molecular or cellular changes that can be shown to indicate exposure to, or effects of, toxicants including Hg. Of particular relevance for Hg is the suggestion that evidence of nervous system damage caused by Hg may be seen in the peripheral blood, in the form of autoantibodies produced in response to fragments of damaged nervous system cells. N-acetyl-p-D-glucosaminidase (NAG) is one of a number of possible markers of renal changes in Hg-exposed workers. Elevation of urinary porphyrins, one of the earliest indices of chronic exposure to Hg in lab experiments, was also observed in dentists. Traditional indices of Hg effects, involving measures of behavioral and physiologic processes, are described below.

INDICES OF EFFECTS

Clinical manifestations

The kidney appears to be the critical organ for exposure to inorganic salts. The earliest change is proteinuria. Hg in all forms accumulates in the kidney and affects tubular and glomerular functions. Recovery of Hg-induced renal impairment is possible if the damage is not too great. Renal effects have been reported with chronic high-level occupational exposure to Hg vapor, in workers with intermittent exposure to Hg vapor, and in patients having dental amalgams. However, a later study found no association between amalgams and renal problems. Neurotoxicity is the dominant feature of many Hg toxicity cases. Although steps have been taken to reduce exposures to Hg, improvements in testing have documented subtle neurobehavioral effects from low exposures that previously had been considered safe.

Occupational exposure to elemental Hg vapor has deleterious effects on visual-motor performance of adults. Two adolescents accidentally exposed to Hg vapor exhibited long-lasting deficits. Tremor was a consequence of substantial occupational exposure to Hg vapors, but was not significant in workers whose exposure was lower and intermittent. Studies of people have generally been confirmed by experiments with laboratory animals. Studies with animals are necessary to observe the effects of Hg without the influence of potentially confounding variables and to examine in detail the cellular effects of Hg on organs. Emotional changes are probably the most commonly reported psychological symptom at a low level of chemical exposure. Affective changes, sometimes referred to as "erethism," have been frequently reported in Hg-exposed people. These changes begin with mild disorders such as anxiety and timidity. In more severe cases, there are personality changes, socially inappropriate behaviors, and performance deficits. One of the most consistent findings in adults exposed to Hg vapor is slowed sensory nerve conduction velocity. Paresthesia, hypothesia, and tremor are commonly part of the clinical picture of Hg poisoning. Constriction of the visual field and other visual impairments are the result of damage to the central nervous system.

The toxicity of Hg is particularly severe during the earliest stages of prenatal and postnatal development. Cell migration and differentiation are easily disrupted by exogenous chemicals. The toxicity of Hg is also important at the end of the life span, when a critical

body burden is attained after years of gradual accumulation of chemicals, and when the nervous system's reserve capacity has been diminished by cumulative loss of cells. The Japanese and Iraqi tragedies illustrates the special vulnerability at the early and late stages of the life span.

Hg compounds are not carcinogenic in humans. Although evidence that Hg can affect the human immune system is sketchy, effects in animals justify further studies. A problem is that these effects appear to be quite variable. Hg has been associated with autoimmune diseases of the kidney and scleroderma. Intestinal bacteria may become resistant to Hg, and this resistance may be linked to resistance to antibiotic medication.

CHELATION THERAPY

Chelating agents have been used clinically as an antidote for severe toxicity of Hg. However, there is limited evidence of the safety and efficiency of chelating drugs to warrant their use for extended durations, for less severe cases, or for prophylactic treatment. Most studies have evaluated chelation outcome in terms of the metal's concentration in blood and other exposure indices; there is less evidence to indicate that chelation restores impaired function in the renal or nervous system toxicity of Hg. Many of the neurobehavioral sequelae of Hg poisoning appear to be irreversible, and the severity of neurotoxicity is influenced by the duration of exposure as well as the magnitude of exposure. Thus, chelation or rehabilitation therapies may be useful only if administered in the early stages of intoxication, before irreversible changes occur. Numerous clinical case reports tell of apparently irreversible neurotoxicity of Hg that survives brief chelation treatment.

The most promising chelators are the dimercaprol derivatives, meso-2,3,-dimercaptsuccinic acid (DMSA, succimer) and dimercaptopropanesulfonate (DMPS, Dimaval). DMSA and DMPS have advantages over chelatmg agents used previously for the treatment of Hg toxicity, e.g., BAL (British anti-Lewisite, dimercaprol), EDTA (ethylenediaminetetraacetic acid), and D-penicil-lamine. DMSA and DMPS are water-soluble derivatives of BAL and thus may be administered orally; they are less toxic than most other chelators, and are effective in reducing metal concentrations in experimental studies, and in reports of clinical efficacy. It is not yet clear whether DMPS or DMSA may be the more effective. More evidence is needed to determine if chela-tors are capable of reversing the toxic effects of metals in the brain and kidney.

Questions about Chelation Therapies

Several aspects of chelation therapy may pose risks to the patient. Chelation may cause redistribution of the metal, resulting in renewed exposure as a result of the liberation of bound metal. Chelation, during ongoing exposure, may enhance the absorption of Hg. Although chelation seems appropriate for the victim of severe poisoning, it is not clear whether chelation is appropriate for patients having less severe intoxication. The most questionable practice is administering chelation for "detoxification therapy," for patients who complain of subtle problems that are nonspecific, and for which no apparent cause has been identified. Some physicians, aware that Hg from amalgams may enter the body by absorption through the buccal mucosa, via the lung and digestive tract, refer to an allergic-toxic syndrome attributable to the accumulation of Hg and other metals in the body. They are administering chelators to people whose complaints include signs and symptoms that could be attributed to Hg. There is no solid scientific evidence to support such chelation therapy.In "diagnostic chelation," administration of the chela-tor may be useful in revealing evidence of a significant body burden after Hg can no longer be detected in urine or blood. However, it is not yet clear how useful diagnostic chelation may be or whether its benefits exceed its risks.

Ключевые слова: ртуть, профессиональные отравления.

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Summary.

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ПРОФЕССИОНАЛЬНЫЕ ОТРАВЛЕНИЯ РТУТЬЮ

В лекции приводятся основные данные о растространенности и встречаемости химического элемента ртуть, рассматриваются некоторые аспекты ее использования в промышленности и связанные с этим возможности отравления. Приводятся основные симптомы и меры борьбы с возможными отравлениями, а также рассматриваются меры безопасности при работах с ртутью.