

CHAPTER 8

Heavy Metal Intoxication

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Introduction

Although some debate exists as to the subject, elements which are classified under 'heavy metals' have come to be those which pose a threat to humans in terms of toxicity. Intoxication with heavy metals is not a typical diagnosis as it is fairly uncommon. This can impose a risk on people who fail to be diagnosed and removed from the source of exposure, increasing morbidity and mortality.

For the purposes of this chapter, in order of atomic weight, the following metals will be discussed: Aluminium, Chromium, Selenium, Silver, Cadmium, Mercury and Lead. A brief introduction of each element's chemical and physical properties will be given, as well as its sources in the environment and any uses. Each metal's toxicity will be illustrated using several actual cases of poisoning. In instances where human cases are not available, animal studies will be discussed. Any treatments for intoxication will be explained at the end of each section.

Aluminium

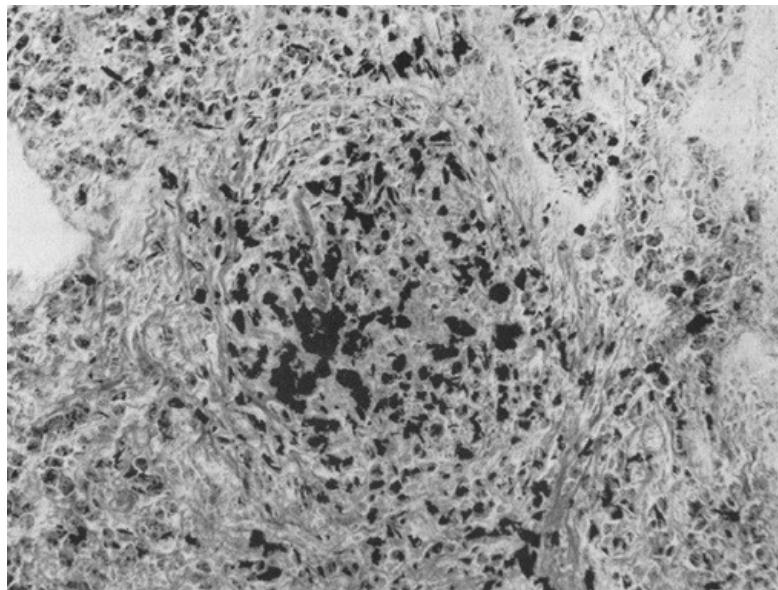
Aluminium (chemical symbol Al) is a member of Group III and can be found in the second period. As a metal, it is silver-white in colour, ductile and malleable. An aluminium oxide layer forms on its surface when it is exposed to the air, protecting it from further reactions. Al in compounds can be found in its +3 oxidation state (Keith, Jones, Rosemond, Ingerman & Chappell, 2008). This element is broadly distributed throughout the earth's crust and it is the most profuse of the metals. In nature, it is found bound to other elements as it is highly reactive. Industrial extraction of Al utilises the mineral bauxite (Keith et al., 2008).

Uses span crockery like pots and pans, as well as beverage cans, airplanes, roofing, siding and foil. Its compounds are used in fireworks and explosives, as well as alums and alumina. Consumer products with Al-compound content include astringents, additives to food, antacids, buffered aspirin, cosmetics and antiperspirants. Human exposure to Al compounds typically occurs from food items or consumer products (Keith et al., 2008).

Toxicity

The reports regarding the health effects of Al are mixed. In a case report by McLaughlin, Kazantis, King, Teare, Porter, & Owen (1962), the deteriorating health of a 49-year old man who had worked in a ball-mill room of an Al powder factory for thirteen and a half years was described. The man showed notable lung fibrosis (Figure 1) caused by inhalation of Al particles from his workplace, but his symptoms were largely neurological.

Figure 1: Photomicrograph of a histological preparation of lung tissue with fibrous tissue in concentric circles visible around particles of Al



Source: McLaughlin et al. (1962)

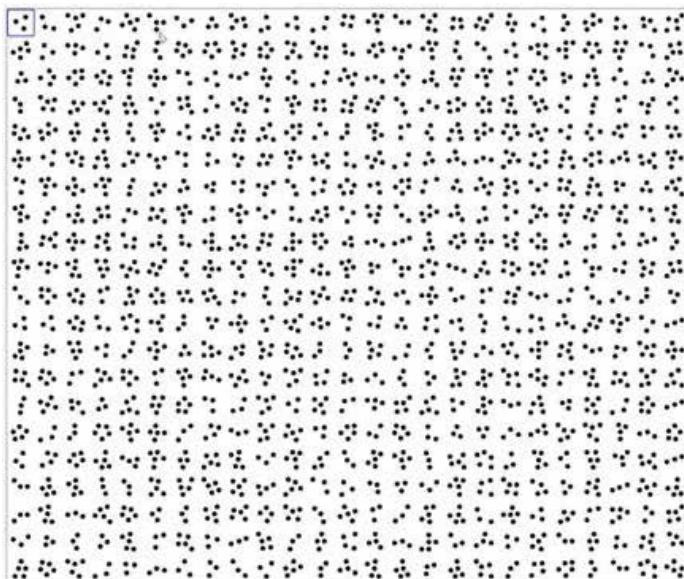
The man's symptoms started with clonic jerking that progressed from the left leg to the left arm, during which attacks he was not capable of speaking. Other symptoms were moderate nominal aphasia and spastic left hemiparesis of the face, arm and leg. His condition progressed with multiple focal convulsive attacks with total aphasia, full convulsions and coma. A minute right embolus in his lung developed, increased mental deterioration and death. His cause of death was bronchopneumonia (McLaughlin et al., 1962).

In this case, the patient's encephalopathy was believed to be the result of Al poisoning. Particles of Al may have been taken up largely from the lungs the partly from the

gastrointestinal tract (McLaughlin et al., 1962).

In a study by Akila, Stollery, & Riihimäki (1999), some neurodegenerative effects were observed in Al workers. Al exposure was quantified from its concentration in the urine of each individual. These individuals were then classified in one of three categories; reference, low and high exposure. They were asked to perform several tasks to establish if there was any neurodegenerativity. Scores indicated no issues with all of the tasks except for two; the Bourdon-Wiersma Dot Cancellation Task and backward counting. The Bourdon-Wiersma Dot Cancellation Task comprises of rows of black dots in groups, of which groups of four dots need to be identified and struck out (Figure 2).

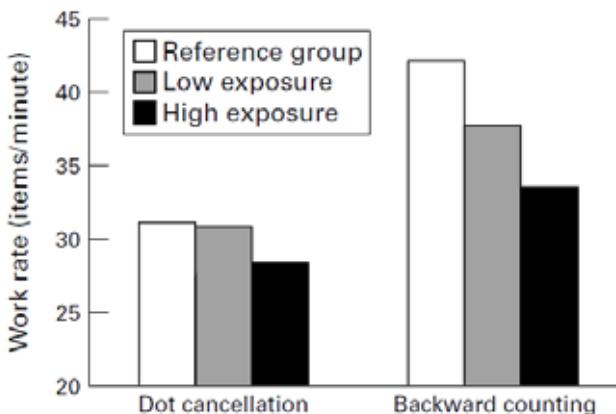
Figure 2: Appearance of the Bourdon-Wiersma Dot Cancellation Task Sheet



Source: Gresham (2012)

In the second task, the individual is given a three-digit number and he or she needs to count backwards in decrements of one. The tasks are both timed at one minute. Workers who experienced the lengthiest exposure to Al scored the lowest (Figure 3).

Figure 3: Bar charts showing the performance (work rates) of different groups of workers classified by the length of their exposure in two tests: the Bourdon-Wiersma Dot Cancellation Task, which comprises in looking for and crossing out groups of four dots among rows of groups of two, three and more dots; and backward counting tasks, which comprises in counting backward from a three digit number in decrements of one.



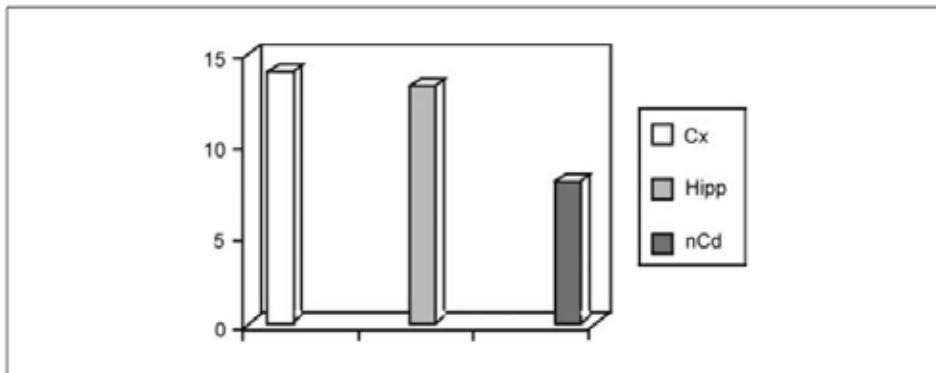
Source: Akila et al. (1999)

These results seem to indicate that Al exposure leads to the detriment of specific cognitive functions, specifically those involving visual-spatial efforts and processing within a time limit.

In a study performed on desert mice, acute intraperitoneal injections of Al caused oxidative stress on the brain. This was deduced from the reduction in activity of the enzymes Superoxide dismutase (SOD) and Glutathione reductase (GR). Both SOD and GR function by breaking down compounds which would otherwise cause oxidative stress on cells. A larger decrease in mitochondrial SOD was noted, in comparison to the decrease in tissue SOD. An increase in malondialdehyde (MDA) proportional to the dose of Al³⁺ was also noted. MDA is a biomarker of oxidative stress (Milovanović et al., 2013).

Figure 4 depicts the index of maximal damage (IMD) which was calculated for the effects of Al. It takes into consideration the reduction of SOD and GR as well as the increase in MDA (Milovanović et al., 2013).

Figure 4: Graph showing the IMD to the cerebral cortex (Cx), hippocampus (Hipp) and nucleus caudatus (nCd) caused following intraperitoneal Al injection in desert mice



Source: Milovanović et al. (2013)

Treatment

The literature was limited with regards to chelation or any treatment for Al poisoning, especially as any pathophysiology of Al intoxication is not yet fully understood.

Chromium

Chromium (chemical symbol Cr) is a transition metal which exists in a number of oxidation states, varying from -2 to +6. The most prevalent are the trivalent and hexavalent forms. In nature, elemental Cr is not found, but it can be mined from its chromite ore with the help of aluminium, silicon or carbon, after which it is purified. Chromite ore can be roasted with soda ash to produce the chromate and dichromate salts of sodium, which are then used to produce other compounds of Cr (Wilbur et al., 2012).

Cr (III) is thought to be a vital nutrient in the human metabolism of fat, protein and glucose. It is believed to function by potentiating insulin. There is some controversy surrounding its status as an essential nutrient as its mechanism of action is unknown (Wilbur et al., 2012).

The industrial uses of Cr include metallurgic, chemical and refractory uses. Stainless steel, nonferrous alloys and alloy cast irons all contain Cr. Refractory applications of Cr include magnesite-chrome bricks, chrome-magnesite and chrome. Chemical industry uses of Cr compounds include pigments, metal finishing, leather tanning and preservatives for wood.

A dietary supplement called chromium picolinate is given with the intention to lessen the symptoms of hypoglycaemia and type II diabetes. This compound consists of trivalent Cr in a complex with picolinic acid (Wilbur et al., 2012).

A meta-analytic study by Bailey (2014) concluded that given Cr supplements has no benefit except in populations who are vulnerable to Cr deficiency, such as patients relying on parenteral nutrition. No effect on fasting glucose levels was found.

Toxicity

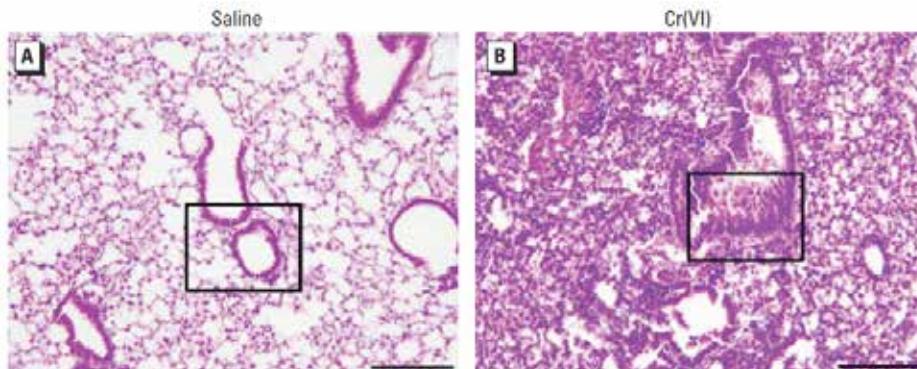
In a number of studies, people living in areas contaminated with Cr (VI) showed haematological, respiratory and gastrointestinal issues. Changes in the complete blood count included a heightened red blood cell count, decreased mean corpuscular volume and decreased platelet count. These results are in agreement with the results of exposure studies conducted on rats (Sharma et al., 2012).

In relation to gastrointestinal issues, reports mention abdominal pain, reduction in appetite and diarrhoea, as well as reports of increased incidence of stomach cancer deaths. Cr (VI) has also been reported to worsen cases of existing dermatitis when taken orally; also, almost twice of dermatological complaints came from females rather than males, possibly due to the regular exposure from polluted sources while performing everyday household tasks. Workers who were exposed to Cr at the workplace complained of eye problems. Populations living in areas contaminated by Cr (VI) also reported respiratory disease and death related to lung cancer (Sharma et al., 2012).

Repeated exposure to Cr (VI) particles was shown to cause chronic inflammation in lung tissue, resulting in neutrophils, macrophages and lymphoid cells aggregating in the epithelial tissue to correct the damage. Reactive nitrogen and oxygen species released by these cells are thought to create a microenvironment that promotes the direct damage of DNA or alternatively hinders DNA repair mechanisms (Beaver et al., 2009).

Chronic inflammation has been linked with the development of cancers, including cancer of the lung. Since repeated exposure to Cr (VI) results in chronic inflammation, this may lead to the development of lung cancer (Beaver et al., 2009). In a monograph about Cr (VI) and its compounds, issued by the International Association of Research on Cancer, the exposure of Cr (VI) is associated with a definite increase in lung cancer risk. Figure 5 shows uncontrolled cell growth following repeated exposure to Cr (VI). Reports regarding nasal cancers seem to indicate that there is a link, however this is less clear (Aitio et al., 2012).

Figure 5: Lung histological sections after the fifth administration of saline (A) and Cr (VI) (B). In the case of B, there is a visible increase in the number of cells, which confirms the likelihood of the carcinogenicity of Cr (VI)



Source: Aitio et al. (2012)



Treatment

Lee et al. (2015) investigated the possibility of treatment for Cr (VI)-induced dermatitis with N-acetylcysteine (NAC). Cr (VI) injected in guinea pig skin resulted in hypersensitivity mediated by an increase in cytokine-dependent reactive oxygen species (ROS). Therefore, the use of an antioxidant such as NAC could prevent hypersensitivity by attenuating ROS production. The effects of NAC include the inhibition of several kinases which in turn results in gene-suppression of a number of cytokines including Interleukin-1. Another pathway by which NAC could mitigate hypersensitivity caused by Cr (VI) is through the prevention of apoptosis and autophagy. This is mainly due to the highly regulated nature of these processes and their uncontrolled occurrence in pathophysiological conditions. Cell death of epidermal keratinocytes is an important mechanism in the development of cutaneous inflammation. Apoptosis and autophagy were both confirmed to occur in Cr (VI)-treated keratinocytes.

Despite these findings, Lee et al. (2015) concluded that although NAC has promise in the prevention of the progression of Cr hypersensitivity, further studies are required to assess cost-effectiveness, compliance and desensitization from prolonged use. The exact mechanism of action of NAC is not fully understood and more research would be required for better comprehension.

Selenium

The non-metal Selenium (chemical symbol Se) can be found in Group VI on the periodic table. It is a necessary micronutrient which can be found throughout the environment. Anthropogenic processes like coal combustion release Se; the natural weathering of Se-rich rocks and soils, as well as volcanic eruptions are also responsible for Se release (Risher, McDonald, Citra, Bosch, & Amata, 2003).

Since Se occurs in the diet, exposure to it happens mainly by ingestion of its compounds, which are both organic and inorganic. The organic components are largely the amino acids selenocysteine and selenomethionine, which can be consumed in cereals, forage crops and grains. Inorganic dietary Se includes selenate and selenite, although the gastrointestinal uptake of these compounds is less efficient than uptake of organic compounds (Risher et al., 2003).

The functions of Se are various. Most Se-containing proteins have antioxidant roles, with some having more precise functions such as thyroid hormone metabolism, Se-protein biosynthesis and spermatogenesis (Roman et al., 2014). In China, Se deficiency has been known to cause a form of cardiomyopathy termed Keshan Disease, as well as a dystrophic osteoarthritis and spondylarthrosis called Kashin-Beck Syndrome (Müller & Desel 2010). Not all Se-proteins have an understood role. Se insufficiency is associated with diseases such as cancer, cardiovascular problems, diabetes and immune disorders. The consumption of excess Se leads to toxicity; in some cases, even sub-toxic doses may result in a negative impact. An example is the increased risk of type II diabetes (Roman, Jitarub & Barbante., 2014).

Toxicity

The symptoms of Se poisoning have been described as nausea, vomiting, dizziness and headaches lasting for a number of days; followed by substantial hair loss after two weeks and fingernail discolouration (Figure 6).

Müller & Desel (2010) described a case of Se poisoning in a 46-year old woman who was otherwise healthy. After consuming a handful of paradise nuts at a work outing, she developed the aforementioned symptoms in addition to cramps, restlessness and fatigue. *Lecythis ollaria*, known as paradise nuts, typically have a very high seleno-cystathioneine content as a result of their growth in soil rich in Se, which can be found in South America. In this case, there was no particular therapy performed and the patient's symptoms subsided after 12 months, although she suffered from distress and anxiety due to her symptoms.

A similar case reported by MacFarquhar et al. (2010) listed the same symptoms. Here, a liquid supplement containing excess Se resulted in 201 cases of poisoning in people who consumed it. As in the other case, the persistence of symptoms was noted a long time after exposure ended. Examples of persistent symptoms included hair loss and nail changes, but mood swings, loss of memory, weakness, musculoskeletal problems and garlic breath were also reported.

Figure 6: Discolouration of the fingernails in a greyish tone due to Se intoxication



Source: Müller & Desel (2010)

Treatment

The current literature does not offer any treatment options in cases of Se poisoning, other than removal from the source of exposure.

Silver

Silver (chemical symbol Ag) is a transition metal with several uses in its elemental form. These include decorative jewellery, ornaments, and silverware such as cutlery and cups. Photographic material using Ag was a leading source of this metal's delivery into the environment. Ag and its compounds are also found in sites for hazardous waste, in combination with soil and water (Abraham et al., 1990).

Great quantities of Ag are liberated into the environment from the natural wearing of rocks and soils bearing Ag, facilitated by processes like wind and rain. This can be carried for a considerable distance and can contaminate groundwater (Abraham et al., 1990).

Ag has been historically used as an antibiotic in various applications. Early writings describe its use in the purification of drinking water. Current uses include bone prostheses, cardiac devices, wound care, orthopaedic surgery involving reconstruction, surgical appliances and catheters. Ionizable Ag is utilised in the clinical setting by incorporation into fabrics to prevent nosocomial infections and improve hygiene (Lansdown, 2006).

Ag exists as two isotopes; ^{107}Ag and ^{109}Ag . Of its three oxidation states, only compounds of Ag^+ are medically relevant. This ion shows interaction with a variety of anions including proteins and receptors on human, bacterial and fungal cells. Ionization of Ag occurs in the presence of tissue exudate and other body fluids, facilitating antibiotic action and absorption (Table 1).

Table 1: Examples of compound containing Ag and their relative capability to ionize

Compound	Ionizing capacity
Metallic silver (incl. nanocrystalline forms and silver coatings)	low ($< 1 \text{ g}\cdot\text{ml}^{-1}$)
Phosphate	moderate
Nitrate	very high
Chloride	low
Sulphate	moderate
Zeolite	?
Sulphadiazine complex	high
Colloidal silver preparations	moderate to high
Allantoinates	?
Oxide (Ag_2O)	low

Source: (Lansdown 2006)

Ag^+ shows strong binding to biological ligands containing sulfur, nitrogen and oxygen (Lansdown 2006).

Silver in wound care

Ag is used in antibiotic prophylaxis or treatment for skin infections such as those in wounds and burns, as well as in transplant surgery. Ag-impregnated wound dressings utilize elemental Ag, silver nitrate and silver sulphadiazine. Wound bed preparations ensure adequate balance between pathogen control and the patient's natural flora, especially in cases of chronic wounds. Free Ag ions are released in response to the presence of tissue exudates and other wound fluids. These ions then execute their antimicrobial function and also absorbed into tissues (Lansdown, 2006).

Dressings impregnated with Ag nanoparticles (AgNPs) have been studied to assess their potential for reducing bacterial biofilm formation. Biofilms are consortia of bacterial growth which offer the colony a much larger survival advantage when compared to planktonic bacteria, which are bacteria floating as single cells in water. A biofilm can be defined as a colony growing within a secreted matrix; advantages of this modality include metabolic cooperation, a larger gene pool and passive resistance. Biofilms exhibit a significant increase in resistance to antibiotics (Velázquez-Velázquez et al., 2015).

A study regarding the utilisation of AgNPs in wound dressings and its potential to control bacterial growth showed that biofilms of *Pseudomonas aeruginosa* could be successfully eliminated by the use of AgNPs. The proposed mechanism of action of AgNPs is the inhibition of extracellular matrix formation in the biofilm (Velázquez-Velázquez et al., 2015).

Silver in catheters

According to a study, Ag-alloy hydrogel urinary catheters were useful in lessening the occurrence of catheter-associated urinary tract infections, known in short as CAUTIs. This study was conducted in acute care hospitals. In comparison to standard catheters, Ag-impregnated catheters reduced infection by 47%, and also reduced the amount of time patients needed to be on antibiotics for CAUTIs (Novotney 2014).

Conversely, in a study by Bayston et al. (2009), Ag-processed catheters used in neurosurgery did not show much promise in bacterial eradication. At high inoculum, Ag had no effect on strains of *Staphylococcus epidermidis*, *Escherichia coli* and methicillin-resistant *Staphylococcus aureus* (MRSA). At low inoculum there was eradication of *S. epidermidis*, incomplete eradication of *E. coli* and no effect on MRSA. The suggested reason for this is the low amount of Ag ions which are available. The possibility of cytotoxicity may result if the quantity of Ag ions is increased.

Toxicity

Repeated consumption or inhalation of preparations containing colloidal Ag result in silver sulfide particles depositing in several organs, such as in the skin causing Argyria and in the eyes causing Argyrosis. The effect of Ag deposits is not dangerous but produces undesirable cosmetic effects (Lansdown, 2006).

Ag is transported via metallothioneins and elimination occurs through the liver and kidneys. Allergic reactions to Ag are a possibility, and therefore the use of antibiotic textiles and medical devices containing Ag is contraindicated in sufferers (Lansdown, 2006).

A case of persistent cyanosis which turned out to be in fact Argyria was reported by Travis (2010). The patient was a 48-year old man who was involved in a car accident which resulted in him being thrown from his motorbike. Following initial stabilization and transfer to the trauma surgical intensive care unit, the patient retained a blue skin tone on his face, torso and arms, with greyish extremities. As vitals and blood gases normalised, this condition persisted and was later diagnosed as Argyria by an experienced trauma surgeon. The levels of Ag in the patient were also thought to have lowered his seizure threshold following intracranial haemorrhage.

Further follow-up with the patient's sister concluded that his Argyria was caused by an Ag-containing preparation and vitamin supplements. The possibility of cyanosis as a diagnosis was excluded (Travis, 2010).

A similar case occurred with a 38-year old man who ingested colloidal silver supplements to treat his joint aches. He went to clinic to address the gray discolouration of his skin (Figure 7).

Figure 7: Greyish-blue skin discolouration (left) compared to normal (right). The patient suffered from Argyria due to his ingestion of colloidal silver to treat joint aches



Source: Wadhera & Fung (2005)

Argyria was confirmed after a punch biopsy of skin taken from the patient's neck was obtained and analysed. The biopsy results showed 1mm granules which were gray-brown to brown-black in colour. These grains were distributed outside cells within the dermis, with concentrations increasing close to the adventitia of eccrine glands (Wadhera & Fung, 2005).

Ag was not believed to result in toxicity in the immune, reproductive, nervous or cardiovascular system, and carcinogenicity was also excluded (Drake & Hazelwood, 2005). However in a more recent study, the cytotoxicity of AgNPs was brought into consideration. It was demonstrated that AgNPs reach the cytoplasm after being phagocytosed by macrophages with the aid of scavenger receptors. Degradation of these nanoparticles releases free Ag ions which hinder mitochondrial function and trigger apoptosis in cells. The results suggested that AgNPs pose a toxicity risk and increased the incidence of inflammation when exposed to mammalian cells (Singh & Ramarao, 2012).

Treatment

The literature was limited with regards to possible ways to prevent Ag toxicity. However, a study performed on Sprague-Dawley rats showed promise in preventing the effects of Ag with concomitant administration of Vitamin E. The effects of AgNP-administration were noted to be prevention of body weight gain and glial-scar formation in the cerebellum (Yin, Yao, Zhou, Faiola, & Jiang, 2015). The results showed that in comparison to control groups, rats given AgNPs gained less weight over the course of 12 weeks. The effect was ameliorated in groups who were also given Vitamin E in combination with AgNPs (Yin et al., 2015).

AgNPs were also observed to cause blood-brain barrier inflammation as well as heightened permeability in the endothelial cells of microvessels. The activation of glial fibrillary acid protein (GFAP) is considered to be an indicator of upcoming biological effects and is related to astrocyte activation. It becomes elevated in situations such as neurodegeneration or acute infection. An increase in GFAP levels was noted in rat cerebella which had undergone nasal instillation of AgNPs, inducing the activation of neuroglial cells together with the degeneration of the granular layer of the cerebellum. These findings suggest that AgNPs demonstrate neurotoxicity *in vivo* (Yin et al., 2015).

Vitamin E is lipid soluble and acts as an antioxidant; it is therefore thought that it can safeguard the brain from oxidative stress. The study showed that Vitamin E treated rats had less GFAP expression and therefore lessened the damage caused by AgNPs. Further studies would be required to assess to what extent Vitamin E can be used to reduced the toxicity of AgNPs (Yin et al., 2015).

Cadmium

Cadmium (chemical symbol Cd) is a transition metal element. Although the pure metal is not typically found in nature, it is associated with zinc ores, and to a certain extent to the ores of lead and copper. For this reason, it is difficult to eliminate the by-product of Cd from the metallurgy of the aforementioned elements. Other industrial sources of Cd include smelting of other metals, combustion of fossil fuels, incineration of waste and the utilization of phosphate and sewage sludge fertilizers (Alexandar et al., 2009).

The uses of Cd in industry include the production of coatings, pigments, plastics, plastic stabilizers, batteries, photovoltaic devices and nonferrous alloys. When it is released in the environment it can contaminate the air, water and soil. Cd is released from natural mechanisms including forest fires, marine aerosol production and volcanic eruptions among other natural phenomena (Faroon et al., 2012).

Typically found in its +2 oxidation state, Cd ions exist in their hydrated forms as well as complexed to organic or inorganic substances. The more soluble forms have the ability to migrate in water, whereas insoluble forms tend to adsorb to sediments and become immobilized (Faroon et al., 2012).

According to data collected in the European Union (EU), it is estimated that 90% of Cd exposure in non-smokers occurs from food, particularly cereals and vegetable crops. Plants can take up Cd salts from the soil. This uptake depends on factors such as the type of soil, the solubility of Cd in it and the species of the plant in question. Other sources of exposure include meat and fish, although these are less significant. However, consumption of organs such as liver and kidneys from exposed animals contributes a more noteworthy source of Cd, as the element tends to accumulate in these organs. For non-smokers, air and water pose negligible threats in terms of exposure as very low levels are present (Alexandar et al., 2009).

Data collected in the United States (US) complies with the report issued by the European Food Safety Authority. Exposure to non-smokers in the US is largely from the diet, with females exhibiting a larger uptake of Cd from their gastrointestinal tract than males. The highest amounts of Cd were found in leafy vegetables such as spinach and lettuce, and in staple foods like potatoes and grains. Naturally high levels of Cd can be found in peanuts, soybeans and sunflower seeds (Faroon et al., 2012).

Smokers showed an overall high mean blood Cd compared to non-smokers. This could be measured as high as 1.58 μ g/L, compared to the average value for adults, 0.38 μ g/L. The

reason for this markedly high value is the fact that tobacco leaves naturally accumulate Cd more readily than other plants. It was also noted that non-smokers exposed to second-hand smoke were also at risk for Cd accumulation (Faroon et al., 2012).

Cd biomarkers are typically detected in blood, urine, hepatic tissue, faeces, renal tissue, hair and other tissues (Faroon et al., 2012). Blood Cd levels tend to be more closely related to recent Cd exposure, whereas urine Cd levels reflect body burden over lengthy exposure, and tend to increase with renal tubular dysfunction. Liver Cd levels are also related to duration and intensity of exposure regardless of renal function (Roels et al., 1981).

Toxicity

This metal ion can pose numerous health risks. Cd²⁺ does not have any known use in animal or human biology, however its divalent nature can assimilate roles performed by other essential metals. It can cross membranes using metal transporters. When it gains entry within the cell, Cd²⁺ can bind ligands with a particularly high affinity. Clearance is difficult, explaining the long term storage of Cd in intestinal, hepatic and renal tissues. The biological half life of this metal is estimated to vary from 10 to 30 years. Its toxicity stems from its interference with iron, calcium or zinc homeostasis, which are necessary for basic cellular functions (Alexandar et al., 2009).

Acute effects

Metal fume fever is a condition which develops within 48hr of exposure to metal fumes and is typically caused by cadmium oxide, although other metal oxides can also cause it. Patients present with flu-like symptoms with resolution within 24-48h of onset. The pathogenesis is not fully understood; however it is hypothesized that upregulation of proteins releases in response to stress occurs. An example could be heat shock proteins, which are chaperone proteins released in response to hypothermia and other environmental stresses. The advised treatment is immediate removal from the source of Cd exposure, bed rest, antipyretics and treatment for osteoporosis (Malaguarnera et al., 2013).

Chronic effects

Metallothioneins are sulfur-containing proteins rich in the amino acid cysteine, which typically bind metal ions in the body; with the example of haemoglobin. These chelators have numerous important functions including transport, detoxification, sequestering and metabolism of metal ions. Metallothioneins bound to Cd are reabsorbed in kidney tubules (Nordberg & Nordberg 2009). Renal cortex Cd accumulation results in tubular proteinuria with measurable loss of low molecular weight proteins. These include retinol binding

protein, α -1-microglobulin and β -2-microglobulin. Progression of renal damage results in glucose, amino acids and minerals being lost in the urine. Long term exposure eventually damages the renal glomeruli and results in a drop in glomerular filtration rate. Uraemia can develop in serious cases. Reversibility of Cd-induced tubular dysfunction depends on the severity of proteinuria, which is quantified by the amount of β -2-microglobulin (B2M) in the urine (Table 2) (Nordberg 1998).

Table 2: Levels of B2M in the urine compared with the level of damage achieved and the possibility for reversal (Nordberg 1998)

B2M in urine (μg/g creatinine)	Clinical interpretation
<300	Within the reference interval.
300-1,000	Incipient cadmium tubulopathy, possibly reversible upon cessation of exposure or forerunner a) of accelerated decline of GFR, increased incidence of renal stones.
1,000-10,000	Irreversible tubular proteinuria, GFR may still be normal.
> 10,000	Overt cadmium nephropathy and usually decreased GFR.

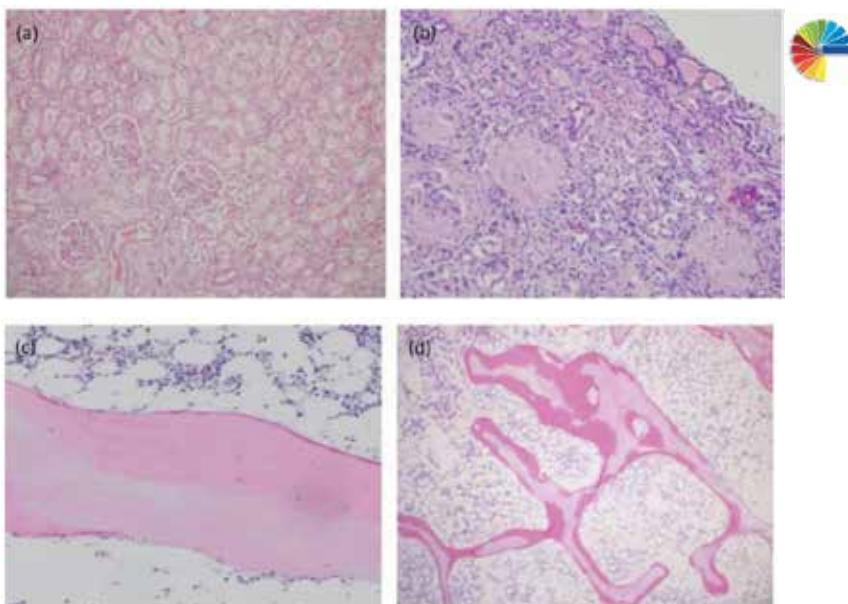
^{a)} this refers to values that have been confirmed in the same subject at least twice in two repeated measurements over a six-month period.

Itai-Itai disease (IID) is a painful disease which presents with multiple distortions and fractures of the long bones. It is the most severe form of chronic Cd poisoning by ingestion. Due to a zinc mine located upstream from Toyama Prefecture, the Jinzu River was contaminated with Cd. People who lived in the river basin showed the symptoms of Itai-Itai (Baba, Tsuneyama, Kumada, Aoshima, & Imura, 2014).

A study conducted on post-menopausal women living in this area. The aim of the study was to link osteomalacia with renal tubulopathy. Two methods for cause of development of osteomalacia were considered; a direct and an indirect pathway. In the direct pathway, osteomalacia is thought to be caused by the direct interference of Cd with bone metabolism. In the indirect pathway Cd causes Fanconi syndrome, which is the damage of the renal proximal tubule resulting in loss of calcium and phosphate in the urine and the subsequent development of osteomalacia. Although the study does not entirely dismiss the direct pathway, histopathological analysis showed that osteomalacia development was linked to the Cd concentration in the renal cortex but not in bone. Figure 8 shows the damage caused by Cd; in comparison to the normal subjects, there is notable atrophy in the renal cortex of IID patients, as well as osteoid lesions in their bones (Baba et al., 2014).

Cd exposure by inhalation has been linked to lung cancer in studies based on men who were exposed to Cd at their workplace; however these studies did not account for other significant factors such as the possibility of other carcinogens or the smoking habits of the subjects. A different studies, it was concluded that Cd was not a cause of lung cancer; rather, cigarette smoking and exposure to arsenic were to blame (Farooq et al., 2012).

Figure 8: Histological sections of normal renal cortex (a), IID patient renal cortex (b), normal iliac bone (c) and IID patient iliac bone (d). Renal cortex atrophy in (b) and iliac bone osteoid lesions in (d) can be observed following prolonged exposure to Cd



Source: Baba et al. (2014)

Treatment

Treatment of Cd exposure is largely symptomatic. Patients exposed to oral Cd salts should be given a gastric lavage or induced to vomit. Inhalation exposure treatment consists of removing the subject from exposure and giving oxygen as necessary. Chelating agents are contraindicated as they are nephrotoxic in combination with Cd (Nordberg, 1998).

In a study using a rat model, administration of *Chlorella vulgaris* was observed to increase excretion of Cd in the urine and faeces, as well as preventing its uptake from the gastrointestinal tract. The precise mechanism by which excretion is increased is unknown. Prevention of Cd uptake is thought to be due to dietary fibre found in *Chlorella*, which traps Cd in the intestinal epithelium. Epithelial cells are then lost in the faeces by desquamation (Shim et al., 2009).

Mercury

Mercury (chemical symbol Hg) is a transition metal which occurs in three variations; the elemental form and in inorganic and organic compounds. In its elemental form Hg is a liquid at room temperature. Depending on how high the temperature, colourless and odourless vapours are emitted (Risher & DeWoskin, 1999).

In its inorganic form, Hg occurs as salts of chloride, sulfide or oxides. A large majority are white salts, with the exception of cinnabar. Cinnabar is mercury sulfide, a red salt which converts to black following light exposure. Organic Hg compounds are also known as organomercurials. The most common organomercurial is methylmercury, a crystalline white solid. Other compounds include dimethylmercury, a colourless liquid, and phenylmercury, a white solid (Risher & DeWoskin, 1999).

In nature the commonest forms of Hg are elemental, mercuric chloride, cinnabar ore and methylmercury. Liquid elemental Hg has multiple uses, such as the production of caustic soda, gaseous chlorine, as well as the extraction of gold from it ore or gold-containing items. Elemental Hg is used in measuring devices like thermometers and barometers, and also batteries and electric switches. Inorganic Hg is used in fungicides, skin-lightening creams, paints, tattoo dyes, topical antiseptics as well as disinfecting agents. Prior to 1991, organic Hg compounds were used in antifungal agents, but this use was discontinued after it became known that Hg vapours were released from these products (Risher & DeWoskin, 1999).

Hg constitutes about 50% of the components of dental amalgam. Other metals include silver, copper, tin and trace metals. Dental amalgam is used to treat dental cavities. Its continued use until today is mainly due to its quality and the fact that most dentists are trained to use it, as opposed to other modern substitutes. These fillings leach Hg when they are being inserted, removed, as they deteriorate with time and from the buried or cremated remains of people who had these fillings. According to the final report prepared for the European commission, the phasing out of Hg-containing dental amalgam would be difficult for a number of reasons, including the expense of dental amalgams that do not contain Hg. Also, dentists would require training to insert these amalgams as well as new equipment with it. Health services in the EU do not always cover these costs; dental fillings are not covered by the national health insurance schemes in Malta (Mudgal, Van Long, Mitsios, Pahal, De Toni & Hylander, 2012).

Toxicity

Hg poisoning in the clinical setting is largely due to suicide attempts by ingestion of mercury cyanide or other compounds. Accidental poisoning is not usual, although reports of Hg exposure by youngsters from broken mercury thermometers and barometers have been reported. Inorganic Hg compounds in their pure powder form are the cause of non-fatal poisoning in adults (Triufante, Soares, Santos, Tavares, Carmo & de Lourdes Basto, 2009).

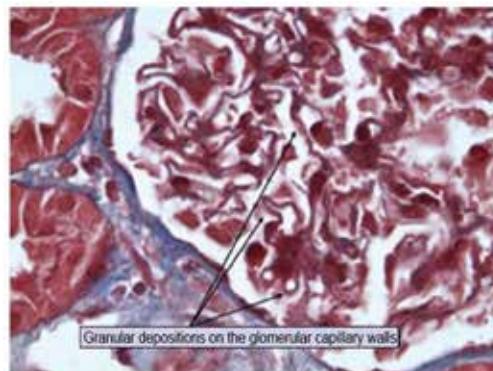
Chronic exposure of methylmercury from bioaccumulation in fish is a cause of concern (Triufante et al., 2009). Hg in trace amounts dissolves in water and is converted into toxic methylmercury, which is absorbed by fish through the gills and by consuming smaller aquatic organisms contaminated by Hg. Larger fish carry the largest amounts of Hg due to predation. A study conducted in Ghana analysed the content of heavy metals including Hg in several canned fish products. Canned tuna brands showed the highest Hg levels from the fish analysed (Okyere, Voegborlo & Agorku, 2015).

Intoxication from inhalation of metallic Hg vapour typically results in respiratory distress which can result in death if severe (Triufante et al., 2009). When Hg is inhaled, 74-80% of the dose is absorbed via the alveolar membrane in the lungs. It is then transported to a number of tissues including the liver, central nervous system and especially the kidneys. In a case report by Gul Oz, Tozlu, Siddika Yalcin, Sozen & Sain Guven. (2012), a family of four suffered varying degrees of Hg poisoning after one of the children brought home a minute piece of Hg in a glass from school, which broke and was vacuumed up by the mother in a non-aerated room.

Nephrotic syndrome due to Hg intoxication developed in the mother following 3 months from exposure. Kidney malfunctions present with proteinuria, which can be for one of two reasons: antigen-antibody complexes that form as a result of excess Hg are not effectively cleared and result in damage to the glomeruli (Figure 9); alternatively Hg ions cause direct damage in renal tubules (Gul Oz et al., 2012).

The initial effects of Hg poisoning are flu-like symptoms within 1 to 3 days of exposure. These effects include excess salivation, oedematous gingiva, fever, dry cough, diarrhoea, nausea and vomiting. Later effects include noncardiogenic pulmonary oedema as well as pneumothorax. In post-mortem analyses of Hg-exposed lungs, damage such as intense corrosion of the bronchiolar epithelium and necrotizing bronchiolitis with fluid accumulation in the alveoli and the interstitium. Dysfunctions in other systems such as the kidneys, liver, blood and skin have also been reported (Gul Oz et al., 2012).

Figure 9: Histological section showing depositions on the capillary walls of glomeruli made up of granules formed by antibody-antigen complexes that did not clear successfully



Source: Gul Oz et al. (2012)

The final phase of Hg poisoning is typically a progressing hypoxic state which can lead to death. If the patient survives the intoxication, there may be residual damage in the form of gingivostomatitis, tremors as well as erythema, which can manifest as loss of memory, emotional instability, insomnia, depression and shyness (Gul Oz et al., 2012).

Injection of metallic Hg with the intent of suicide is also reported. Intravenous injection leads to pulmonary embolization by globules of Hg, and patients present with chest pain, dyspnoea, fever and cough. Other signs include changes in the patient's electrocardiogram, impairment of renal function and dermatological symptoms. Subcutaneous Hg injections results in inflammation that is localised, granulation tissue and the formation of abscesses. Eventual systemic involvement is also expected (Alhamad, Rooney, Nwosu, MacCombs, Kim & Shukla, 2012).

In case of methylmercury poisoning, effects on the cardiovascular system may be reported. This can be easily confused with pheochromocytoma, a catecholamine-secreting tumour which also presents with hypertension and tachycardia. The common factor is accumulation of catecholamines. In case of inorganic Hg intoxication, Hg incapacitates the cofactor of catecholamine-O-methyltransferase, which is the enzyme that is responsible for catecholamine degradation (Gul Oz et al., 2012).

Tachycardia and hypertension can fall under acrodynia, which is a collection of symptoms resulting from Hg poisoning, that also include mental changes, swelling and

irritation of palms and feet with skin desquamation, extreme sweating, pain localised in the extremities, photophobia, anorexia and fever (Gul Oz et al., 2012).

Treatment

British Anti-Lewisite, also known as BAL, was developed in warfare as an antidote to lewisite, which is an arsenical vesicant. BAL's chemical name is 2,3-dimercaptopropanal, and it is an oil which is freely absorbed by the skin. It binds lewisite to form a stable compound, therefore removing this toxin's effect on the enzyme pyruvate. BAL can also prevent the vesicant effects of lewisite if applied before exposure, but can reverse the initial symptoms up to two hours after exposure. The resulting compound is then excreted in the urine. This drug was also used to treat Hg poisoning (Peters, 1949).

In rats, intravenous BAL proved effective in preventing the acute systemic poisoning caused by mercury chloride. When BAL was supplied by injection as well as oral dosage, it also safeguarded the rats from fatal doses (Stocken, 1946).

In the 1950s, chemically similar dithiols which could also dissolve in water were produced; unithiol (DMPS) and succimer (DMSA). Treatment with these substances is required as early as possible following Hg exposure, as their effectiveness decreases with time. In chronic intoxication, DMPA and DMSA chelation appears to reduce the inorganic Hg burden on some organs. However, in morbidity and mortality terms, the benefit has not yet been concluded. Some observed side effects of DMPS and DMSA include allergic reactions with widespread rashes in 1 to 10% of subjects in certain studies. Other effects include gastrointestinal issues and reversible rises in hepatic transaminases and drops in white blood cell count (Kosnett, 2013).

Lead

Lead (chemical symbol Pb) is a group IV element of the periodic table. It does not occur in particular abundance, however its ores are easily accessible and found in several locations the world over. These ores include Galena (PbS), Cerussite (PbCO₃) and Anglesite (PbSO₄). Its physical properties include resistance to corrosion, relatively large density and low melting point. Pb's oxidation states include the elemental form, Pb²⁺ and Pb⁴⁺, with the (II) oxidation state being the most abundant in nature. Metallic Pb does exist but it is rare. Some organolead (IV) compounds also exist (Abadin et al., 2007).

Pb's uses include solder, weights, pipes and storage batteries. The largest availability for human exposure stems from the past use of Pb as a gasoline additive which caused a broad environmental dissemination. A second source of likely exposure comes from

paints containing Pb pigments. In the US, the use of Pb in gasoline was phased out and stopped by 1995. The use of Pb paints became illegal in 1978, however older homes still had leaded paint. As this type of paint peels off, Pb dust is released and is a potential route of exposure to Pb. Some exposure from drinking water which has passed through Pb pipes and fittings also still occurs, although Pb content regulations in pipes were established in 1988 (Abadin et al., 2007).

People working in industries such as Pb smelting and refining, manufacture of batteries, construction, steel, printing, plastics, rubber, radiator repair shops and firing ranges are at a risk for Pb exposure. This is mainly due to flame soldering of solder containing Pb. In these cases, inhalation exposure can occur (Abadin et al., 2007).

Other possible exposure routes include the use of Pb in non-western folk medicine and Pb glazes on ceramic pottery which can leach into food or drinks stored inside them (Abadin et al., 2007).

Toxicity

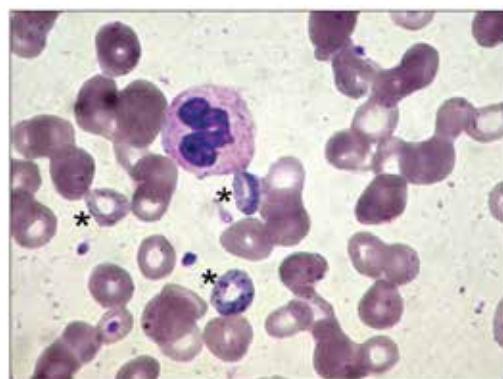
The acute form of Pb poisoning typically occurs by lead acetate. Instantly after being exposed orally to lead acetate, the patient suffers from throat stinging and thirst. This is typically followed by vomiting within 30 minutes. Worsening colic that is alleviated by pressure occurs. Abdominal examination reveals tenderness and contraction. The patient also suffers from oliguria as well as constipation; the stools are dark due to the formation of lead sulphide. The patient is weak with cold and clammy skin, and the pulse is typically fast and weak. Nervous symptoms include insomnia, vertigo, headache, drowsiness, muscle cramps, numbness and convulsions; in some cases also paralysis. Exhaustion can lead to death (Kadu, Nampalliwar, Pandey, Sharma & Gothecha, 2012).

When the poisoning occurs with tetraethyllead, symptoms are mainly nervous while gastric symptoms are less pronounced. Nevertheless, some patients suffer from nausea, vomiting and anorexia. Nervous symptoms are grouped under the umbrella term 'lead encephalopathy'. This includes irritability, anxiety, insomnia, nightmares, headache, excitement, vertigo, tremors, myasthenia, convulsions and delirium. Cardiovascular symptoms are usually bradycardia and hypotension (Kadu et al., 2012).

A case report by Yen, Lin and Weng (2010) describes a 23-year old male who suffered from Pb intoxication. His occupation was Pb battery recycling. The patient was referred due to intermittent and colicky abdominal pain that could not be relieved or worsened by any factors. His abdomen was found to be soft and tender, and no neurological symptoms

were reported. The patient's blood results showed drops in haemoglobin level, haematocrit and mean corpuscular volume, which was diagnosed as microcytic anaemia. Stippling of basophils could be observed from a blood smear: a sign linked with Pb poisoning (Figure 101).

Figure 10: Peripheral blood smear showing microcytic erythrocytes with visible basophilic stippling, marked with an asterisk (*), a sign of Pb intoxication



Source: Yen et al. (2010)

In pregnant women and children, Pb causes a great deal of harm. Pb can traverse the placenta. Fetal Pb levels are usually 75-100% higher than those of the mother. Miscarriage, premature membrane rupture, preterm birth and delay in development are linked with elevated maternal Pb levels. Pb inhibits several enzymes required for the synthesis of haemoglobin, hinders the sodium-potassium pump and binds to the cell membrane of red blood cells, making them fragile (Kadu et al., 2012).

Children with high Pb levels suffer from mental retardation, seizures, coma and death. Lower levels can cause learning disabilities, colic, attention-deficit hyperactivity disorder, hindered growth, loss of hearing and weakness in the upper body. Chronic exposure damages the kidneys, central nervous system and causes blood changes. Syndromes which are Fanconi-like have been reported. In cases of severe, extended poisoning, patient's gums develop a purplish line, however this is not commonly seen. Another typical feature of Pb poisoning is the visibility of 'lead lines' on an X-ray; these areas signify cessated bone growth (Cohen, 2011). These lines were observed in the long-bone X-rays in a case report by Hildebrand (2011). The infant in this case was born after 38 weeks of gestation to a mother who regularly consumed ground Pb-containing pottery. High density bands

could be observed in the child's tubular bone metaphyses, particularly in the distal ulnas and proximal fibulas (Kadu et al., 2012).

Chronic Pb toxicity results in anaemia, colic, constipation, gingival Pb lines, neurotoxicity, peripheral neuropathy, encephalopathy, renal toxicity, cardiovascular toxicity, menstrual problems, spontaneous abortion, developmental defects and carcinogenicity (Kadu et al., 2012).

Treatment

Treatment for Pb intoxication is given by chelating agents. These include 2,3-dimercaptosuccinic acid (DMSA), which is also known as succimer, an analogue of dimercaprol which can dissolve in water. Succimer has a broad therapeutic index which makes it superior to the other chelating agents, CaNa2EDTA and dimercaprol. The structure of succimer consists of four carbon atoms, two sulfur and two carboxyl groups. It clears Pb as the latter binds to the adjacent sulfur and oxygen atoms (Lowry, 2010).

Another chelating agent is DMPS, whose chemical name is racemic-2,3-dimercapto-1-propanesulfonic acid. This water soluble agent has some relation to dimercaprol and DMSA, but it shows less toxicity than dimercaprol. Its formulations include intramuscular, intravenous and oral. DMPS can treat a number of types of heavy metal poisoning, including Pb (Lowry, 2010).

Penicillamine is a degradation product of penicillin, specifically a D-B, B-dimethylcysteine. It is a fairly old drug which was the oral chelator of choice before the introduction of DMSA (Lowry, 2010).

Conclusion

Diagnosis of heavy metal intoxication is not one of the first which comes to mind when presented with a case, and therefore achieving a good standard of care requires understanding the sources of exposure of each metal as well as the pathophysiology of poisoning. This is also true from the point of view of researchers looking for possible prevention treatments.

Elements like Aluminium are used in daily items and exposure at subclinical levels occurs on a regular basis. Selenium and to a certain extent Chromium are micronutrients, although in excess they show toxicity. Silver has multiple uses as an antibacterial agent but can give undesirable cosmetic effects when used excessively or ingested in supplements. Metals like Cadmium, Mercury and Lead show no uses to the body and cause different

degrees of damage to the human body depending on route and level of exposure.

Exposure can occur from medication, diet, environmental contamination and at the workplace. For this reason, a thorough history of possible heavy metal intoxication cases should be gathered and scrutinized before any attempt at a diagnosis is made. The importance is placed on the need for environmental data sensors and capture devices that help identify traces of these elements, which technology was introduced as part of the ERDF156 project that catered for environmental parameters but requires an additional series of element-capture devices spread across the islands to ensure a uniform approach. Such would enable a medico-spatial analysis linking=g trace identification, health and spread of incidents in relation to physical space.

When multiple patients present with similar symptoms, it can be advisable to further investigate any linking factors. The possibility of intentional poisoning as a means of suicide or murder cannot be excluded.

The primary treatment is removing the patient from the source of exposure as soon as possible. Further follow-up depends on the type of metal poisoning; chelating agents discussed in the essay are used at the discretion of the physician in charge, due to side effects and the chance of nephrotoxicity especially when the kidneys have already been implicated.

Future research should be based on the prevention as well as treatment. New and better chelators are a good avenue, however other studies have focused on substances like Vitamin E and NAC, as well as organisms like Chlorella vulgaris for preventing the toxic effects of specific metals when administered concomitantly. More studies would be required before any conclusions can be reached; however, current studies are showing promise.

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