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A Synopsis on Metals in Medicine and Psychiatry

CHRISTOPH Y. YUNG

Department of Psychiatry, Texas Tech University Health Sciences Center School of Medicine, Lubbock, TX 79430

YUNG, C Y *A synopsis on metals in medicine and psychiatry.* PHARMACOL BIOCHEM BEHAV **21:** Suppl 1, 41–47, 1984 —A total of 40 metals are reviewed and summarized to give a general perspective on the metal's two major effects, relevant to medicine and psychiatry in man. These two effects are metal excess (poisoning) and deficiency. These metals are grouped arbitrarily into six categories; (a) The heavy metals, (b) the essential and questionable essential trace elements, (c) the macrominerals, (d) the alkali metals, (e) elements used as therapeutic agents, and (f) miscellaneous elements. The heavy metals are invariably toxic and could be lethal, and no deficiency state has yet been described in man, although arsenic has been postulated to be essential. The essential trace elements are vital to a number of vital physiological and biochemical functions, and newer essential trace elements are to be identified in the future The recent findings suggest vanadium excess may aggravate the affective symptoms in bipolar affective disorder; selenium may inhibit certain carciongenesis such as oesophageal cancer; and silicon may inhibit atheromatous formation in the aorta. There is also some suggestion that certain allergic syndromes may be correlated with very low levels of iron, copper, manganese The study of elements will undoubtedly expand the understanding of disease processes in medicine and psychiatry

Elements Metals Poisoning Psychiatry

METAL deficiencies and excesses (poisonings) have been gaining considerable interest and attention in various health sciences desciplines. This includes medicine, public health and nutrition, environmental pollution and contaminations with industrial chemicals, bioactive and radioactive products. Decades ago, medicine was concerned with the identification, treatment and prevention of metal deficiencies and excesses. Recently, the interests have been focused on investigations related to the role of metals, especially the trace elements, in carcinogenesis, e.g., zinc, selenium and molybdenum; in affective disorders in psychiatry, e.g., lithium and vanadium, and in neurological disorders, e.g., aluminum in dementia. The number of publications on chemically induced neurological diseases has increased considerably during the past decade and therapeutically related toxic reactions from drugs make up the largest reporting group [25].

This paper is a concise overview of 40 elements, serving as a general reference with a broader perspective and interest in the roles of metals in medicine and psychiatry. The basic aspects of the physiochemical and biochemical properties of metals, the metabolic pathways, the clinical manifestations and treatments will not be dealt with The reader is referred to the appropriate source on these specific issues as provided in the references

GENERAL ASPECTS OF METAL

Bonner gave an excellent review on the biochemical properties, metabolic processes and enzymatic reactions induced by metals [3]. Following are aspects of metal properties of clinical relevance.

The whole blood body and brain concentrations of some of the elements to be described in this paper is presented in Table 1. This shows a concentration range from μg to g levels dependent on the element measured. The toxic reactions from metals are frequently the result of their binding to the metabolically active groups i.e., binding sites. These include amino acids, polypeptides, proteins and enzymes. These contain carboxyl (−COOH), phosphoryl ($-HPO_3$), amino ($-NH_2$), imino (=NH), sulfhydryl (thiol) (−SH) and phenolic groups. For example, most of the heavy metals bind the thiol groups, which are binding sites on enzymes, crucial to energy provisions or oxygen transport in cells. Arsenic, mercury, antimony and cadmium bind the sulhydryl group and become highly toxic. The affinity of mercury for binding with these groups is in the following descending order of: SH > $CONH_2$ > NH_2 > COOH > PO_4.

Metals can also affect the concentration and functions of another metal, through several mechanisms. The metal may act as an antagonist to certain functions of other metals. Sulfur is an antagonist to selenium by competing for reactive sites in certain enzymes while zinc and molybdenum are antagoistic to copper. Also, increased intake of either of zinc or molybenum increases the requirement for another metal, i e , copper, and may induce a copper dificiency state. On the other hand, increased sulfate will increase the excretion of molybdenum.

Metal also can affect the bioavailability of other metals or toxicity of trace elements. This occurs when an element resembles another in the atomic structure, which tend to exert antagonistic action. This may explain selenium protection against the toxic effects of excessive zinc and tungsten action against excess selenium intake. In contrast, calcium deficiency can heighten the teratogenic and toxic effect of lead.

TABLE 1
CONCENTRATION OF METALS IN HUMANS

Elements	Body	Brain
Calcium	1000–1250 g	
Phosphorus	670 g	
Sulfur	175 g	
Potassium	140 g	
Magnesium	35 g	
Iron	3–4 g	
Zinc	1 4–2 3 g	
Lithium (Therapeutic dose range)		
Copper	100–150 mg	
Iodine	20–50 mg	
Manganese	12–20 mg	500 micrograms
Nickel	10 mg	
Selenium	1 1 μg/100 ml*	130 micrograms
Vanadium	1 0 μg/100 ml*	45 micrograms
Molybdenum	10–20 mg	20 micrograms
Chromium	6 mg	
Cobalt	1 mg	

*Whole blood

In addition, some metals maintain an equilibrium with another metal. For example, high dietary phosphorus content may lead to high calcium requirement. Therapeutic drugs may also induce alteration in the metabolism of some minerals This is seen in hypokalemia which can be induced by diuretics, salbuamol and certain antibiotics Corticosteriods, phenylbutazone, oxyphenbutazone and carbenoxolone sodium increase sodium retention. Carbamazepine induces hyponatremia, because of the antidiuretic action through its vasopressin-like action. Chlorpropramide induces water intoxication then to hyponatremia Drugs having effects on macrominerals are diuretics which can induce magnesium depletion, and hydroxycholecalciferol which may lead to magnesium intoxication Heparin and steroid may trigger osteoporosis, phenytion and laxatives may cause hypocalcemia and aluminnum hydroxide antacids accounts for phosphate deficiency and osteomalacia [10].

Genetic factors may also play a role in metal toxicity There are certain metal deficiency syndromes which are due to inherited genetic defects, e g , copper dificiency in X-linked Menke's kinky hair syndrome, zinc deficiency in acrodermatitis enteropathia. While copper excess, as in Wilson disease, is due to an autosomal recessive transmission with defective syntheses of ceruloplasmin.

SYNDROME OF METAL DEFICIENCIES AND EXCESSES

Heavy Metals

It is so named due to their greater atomic weight than the physiologically essential elements. Table 2 summarizes the signs and symptoms and source of heavy metal poisoning Six elements have been found to cause toxicity in humans [1, 3, 9]. These are arsenic (As), antimony (Sb), cadmium (Cd), lead (Pb), mercury (Hg) and thallium (Tl) [1, 4, 17, 18, 20]. Chronic lead poisoning is of great importance in pediatrics and child psychiatry Because of its insidious onset, and its clinical features may mimic other medical and psychiatric disorders, chronic lead poisoning could be misdiagnosed as growth and developmetnal failures, hyperkinetic syndrome, and learning disabilities. No known deficiency syndromes in this group has been described in man. However, recent data indicates that As may be an essential element and this suggests that a deficiency syndrome may exist for As [1,21].

Mineral Elements

The term macromineral is used to denote a group of elements which are present in the largest amount in the human body, while "trace elements" consist of those elements present in small amounts Table 3 summarizes the signs and symptoms of maromineral poisoning and deficiency.

These macrominerals include sodium (Na), potassium (K), phosporus (P), calcium (Ca), magnesium (Mg) chlorine (Cl), and sulfur (S) Calcium and phosphorus constitutes three-fourths of the mineral content of the body, as the main structure component of bone and teeth. Iron (Fe) is an essential mineral element, a functional component of hemoglobin, myoglobin, enzyme and plasma iron transport It is stored as ferritin and hemosiderin. It's deficiency causes iron deficiency anemia, and its excess cause hemosiderosis

Trace Elements

Trace elements are all those naturally occuring elements excluding the macrominerals and the bulk elements (hydrogen, carbon, nitrogen, oxygen and sulfur) The trace elements are classified into three categories: (1) the essential trace elements, (2) the trace elements with questionable essentiality, and (3) others The essential trace elements have been established to be vital to human functions as bodily nutrients, which is as important as calories and vitamins

TABLE 2
HEAVY METAL POISONING

Elements	Source	Signs and Symptoms
Arsenic	Contamination in beer, wine	Gastro-intestinal symptoms
	Insecticide	Hyperpigmentation
	Gold-mining	Edema of face
	Well water	Anemia
	Wood preservative	Neurotoxicity
		Neuropathy
Antimony	Smelting	Neurotoxicity
	Helminthic drugs	
Cadmium	Welding	Lung edema
	Soldering steel	Nephropathy
	Cadmium coating	Osteomalacia
	Paint	Itai-itai-byo (ouch-ouch disease)
Lead	Dust	Convulsion
	Car fumes	Anemia
	Paint	Neurotoxicity
	Plastic industry	Encephalopathy
Mercury	Herbicide	Gastrointestinal syptoms
	Explosives	Coma, death
	Electronic industry	Neurotoxicity
		Mental symptoms (Erythism)
		Minamata disease
Thallium	Insecticide	Neurotoxicity
	Rat poisons	Thallitoxicosis
	Denaturing alcohol	

TABLE 3
SIGNS AND SYMPTOMS OF MACROMINERAL DEFICIENCY AND POISONING

Elements	Deficiency	Poisoning
Calcium	Tetany Decreased bone density in newborns Abnormal calcification of bones, teeth Osteoporosis	Impaired respiratory and cardiac muscle functions Milk-alkali syndrome
Phosporus	Dietary deficiency is unknown It is present in nearly all foods Deficiency usually secondary to renal disease, sprue, celiac disease, rickets, osteomalacia, hyperthyroidism	Hyperphosphatemia (no specific signs or symptoms Usually associates with hypocalcemia)
Magnesium	Hypomagnesemia Neuromuscular dysfunction (tremor convulsion) Deficiency secondary to alcoholism, liver cirrhosis, Malabsorption, diuretics	Muscle weakness Coma "Hard water syndrome" from dialysis

They are constitutents of the important molecules such as enzymes, cofactors or catalysts in metabolic processes. The essential trace element poisonings and deficiencies [3, 11, 12, 21, 25, 26, 29, 31, 32] are summarized in Table 4. The trace elements with questionable essentiality are summarized in Table 5. They are essential to animals, however, the proof of its essentiality in man has not yet been established. It is possible that some of these elements may be essential in certain biological processes or certain diseases, as outlined in Table 5. For example, selenium (Se) deficiency has been

TABLE 4

SIGNS AND SYMPTOMS OF ESSENTIAL TRACE ELEMENT DEFICIENCY AND POISONING

Elements	Deficiency	Poisoning
Chromium (Cr)	Impaired glucose tolerance Risk of cardiovascular disease	Least toxic of trace elements Renal impairments Dermatitis Gastrointestinal symptoms
Cobalt (Co)	Pernicious anemia Methylmalonic aciduria (integral part of vitamin B-12)	Cobalt beer cardiomyopathy Polycythemia
Copper (Cu)	Menke's syndrome, blood disorders	Wilson's disease Copper deposits in liver, kidney and brain
Iodine (I)	Hypothyroidism Goitre Cretinism	Thyrotoxicosis
Zinc (Zn)	Acrodermatitis enteropathica Hypogonadal dwarfism Poor wound healing Hypogeusia Hyposmia	As Zinc chloride (Pulmonary disorders)

TABLE 5

SIGNS AND SYMPTOMS OF DEFICIENCY AND POISONING OF TRACE ELEMENTS WITH QUESTIONABLE ESSENTIALITY IN MAN

Elements	Deficiency	Poisoning
Floride	Dental caries	Mottling of teeth enamel Osteosclerosis osteomalacia Renal impairment
Selenium	Keshan disease Kaschin—Beck's disease	"Blind staggers ' (cattle) Selenosis (cattle) (lameness, stiffness, anemia, emanication)
Molyb-denum	Carcinogenesis in breast and probable oesophageal cancer	Goutlike symptoms "Teart syndrome in cattle" (brittle bones, depigmentation, anemia)
Manganese	Defective growth*	Liver dysfunction Neuromuscular disturbance Symptom similar to Parkinsonism
Tin	Growth retardation*	Gastro-intestinal symptoms Neuromuscular disturbance Stannosis (benign pneumonconiosis)
Vanadium	Growth retardation*	Depression or mania in humans' Anemia in animals, damages to liver, kidney, heart
Nickel	Retarded bone growth* Hepatocyte abnormalities*	Neurotoxicity Pneumonitis Hypoglycemia Gastrointestinal disorder Chronic dermatitis Respiratry carcinogenesis
Silicon	Bone and cartilage deformity*	Silicosis Urolithiasis

*Animals

TABLE 6
SUMMARY OF ALKALI METAL DEFICIENCY AND POISONING

Elements	Medical Disorders	
	Deficiency	Excess
Lithium	Not known	Neurotoxicity Renal impairment Electrolyte disturbance Thyroid dysfunction Involves almost all body organs with side effects
Sodium	Hyponatremia Psychogenic polydipsia Syndrome of inappropriate secretion of antidiuretic hormone	Hypernatremia
Potassium	Hypokalemia Aldosteronism Bulimia, anorexia nervosa Renal tubular acidosis	Hyperkalemia Potassium sparing diuretics
Rubidium	Not known	Tetany, convulsion, death
Cesium	Not known	Neuromuscular toxicity convulsion
Francium	Not known	Not known

reported in man, as Keshan disease in China in 1935 [15]. This is characterized by signs of congestive heart failure in children less than 15 years of age, with women of childbearing age being most susceptible. This disease could be reversed by administering Se. There are two reports of cardiomyopathy in humans associated with low blood Se levels reported in the USA [6,14]. Selenium depletion has been reported to occur in inebriated alcoholic subjects [8]. Selenium may also play a role as an antioxidant in reduction of carcinogenesis in breast cancer.

Molybdenum (Mo) is another trace element which has been investigated for its essentiality in man [13,16]. A Mo deficiency state has been studied [14], and it has been postulate that Mo may inhibit the development of breast and esophageal cancer [19]. Vanadium (V) has been found to be an essential element for growth and reproduction in animals, with effects on lipid metabolism and ATPase activity Poisoning has been found in workers exposed to V mining or alloy steel industry, manifesting behavioral and psychiatric symptoms with depression and mania. The effect of V in manic-depressive patients was studied by reducing V levels with vitamin C and low V diet, and resulted in improvement of the illness [22,30]. It has been also postulated that V could be a factor in the severity of manic-depressive symptoms [22,30]. The increasing use of parental nutrition in patients with cancer and gastro-intestional disorders, a deficiency state due to some of these trace elements could become more frequent in medicine [2].

The Other Trace Elements

Aluminum (Al) has been implicated in a severe encephalopathy syndrome in some patients undoing chronic hemodialysis. This is characterized by dementia with speech difficulties, motor dysfunction, loss of muscle coordination, seizures and with fatality. The source of Al is possibly from the absorption of aluminum containing antacids, which are used to bind intestinal phosphate to reduce the hyperphosphatemia in dialysis patients and secondly there seems to be a high concentration of Al in the water of the geographic areas of high prevalence of dialysis encephalopathy [12]. Al excess causes hypophosphatemia. It has been implicated for renal osteomalacia, and Alzeheimer's disease. Some reports showed an increase amount of Al in the brains of Alzheimer's disease patients. However, there are negative studies.

Alkali Metals

Alkali metals are univalent metals occupying Group 1 A of the Periodic Table. They are lithium (Li) sodium (Na), potassium (k), rubidium (Rb), cesium (Cs) and francium (Fr). Sodium and K are essential and vital to life, so much so that either a fall or increase beyond their normal range in their concentrations in the intracellular or extracellular spaces will create a life threatening situation. Lithium has been the drug of choice in the management of bipolar affective disorders, and has been put to clinical trials in no less than 30 medical conditions and 20 psychiatric disorders. The deficiency and excess syndromes for these alkali metals are summarized in Table 6.

THERAPEUTIC ASPECTS

The use of metal as therapeutic agents will extend beyond the current status as replacement of deficiency states, with the increasing understanding of the roles of metals in the biological processes, and the interaction of metals with one

TABLE 7
TOXICITY DUE TO METALS USED AS THERAPEUTIC AGENTS

Elements	Medical Uses	Toxic Effects
Bismuth	Wart A colloid bismuth for gastric or duodenal ulcer	Renal impairment Encephalopathy Agranulocytosis Rickets Osteosarcoma
Gold	Chrysotherapy in Rheumatoid arthritis (sodium aurothiomalate, sodium aurothioglucose)	Dermatitis Stomatitis Renal damage Lung fibrosis
Lithium	See Alkali metal section	
Uranium		Nephrotoxicity
Mercury	Calomel ointment as topical antiseptic	Nephrotoxicity
Cobalt Cesium Radium	As gamma rays in radiotherapy in cancer	Radiation pneumonitis Carcinogenesis Cobalt myocardiopathy in beer additives
Silver	Burns ophthalmic solution (ophthalmia neonatorum)	Argyria
Florine	Dental caries prevention	Fluorosis
Barium	Radio contrast medium	Gastrointestinal symptom Convulsion Hypertension Cardiac arrest

another Table 7 summarizes the toxicity effects of some of the metals commonly used as therapeutic agents In addition to the possible role of Se and Mo in inhibitions of carcinogenesis, there are also other metals which may have anti-cancer activity, such as platinum (Pt) and rhodium (Rh) in the form of ethylenediamine complexes [27] There are numerous vitamine preparations which contain microtrace elements (chromium, selenium and molybdenum) and other minerals (zinc, copper) Herpectin-L, a cold sore lip balm, contains titanium

In addition, there are other metals whose role in humans has yet to be established For example, beryllium (Be) intoxication causes pneumonitis and osteosarcoma in animals has been reported, as well as bone tumors in human. Indium (In), used in electronic industry, is among the most potent metalo teratogens yet studied.

In conclusion there are no less than 40 elements which have been found to have effects on the human biological systems, in addition to the "bulk elements" such as hydrogen, carbon, nitrogen, oxygen and sulfur The major interest and attention at present seems to be focusing on further investigation of newer trace element usages, methods of identifications and the search for a more effective means to induce a deficiency state in the laboratory Evaluation of mechanisms of metal-metal interactions may provide further insight in the properties of these metals and extend beyond the current status of replacement therapy in deficiency syndromes and the prevention of certain medical conditions The investigations on silicon in preventing atheromatous formation in the aorta [5] and selenium in protecting chemically and virally induced malignant tumors, are some examples in these areas.

Moreover, the proven efficacy of lithium in treatment of bipolar affective disorders and its use as mainteneance therapy in both bipolar and unipolar disorders in psychiatry, and the reported trials of vanadium and rubidium in bipolar diseases, may stimulate interest in studying other metals in various psychiatric disorders. Interestingly, hair analysis has been used as a diagnostic tool in children suffering from autism, retardation, epilepsy, hyperactivity, learning difficulties and allergic syndromes, and some autistic children were found to have very low levels of iron, copper, and manganese and others with a comparatively high molybdenum content [3] Thus, certain elements may play a role in certain psychiatric disorders than has been previously accounted for The continued search for the underlying mechanism and biochemical correlates of mental illness may increase our understanding of biochemical factors involved [7]

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