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New Aspects on the Distribution and Metabolism of Essential Trace Elements After Dietary Exposure to Toxic Metals

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ABSTRACT

Under present environmental conditions, an increase in pollution owing to metals such as cadmium (Cd), lead (Pb), and methylmercury (MeHg) must be expected. The resulting effects would be seen particularly in the food chain. The daily intake of toxic metals in various parts of the world is different and depends on both the dietary habits and the concentration in foodstuffs. Oral ingestion of these toxic metals perturbs the metabolism of essential elements, especially zinc (Zn), copper (Cu), iron (Fe), and selenium (Se). The elemental composition of body tissues and fluids is an indicator of the nutritional and pathological status of humans.

This review will describe the dietary intake and gut absorption of essential and toxic elements. Furthermore, it will discuss threshold values, toxic effects in relation to body burden of toxic metals, the biological indices of exposure, and the interaction between toxic and essential elements. The overall ratio of Cu, Zn, Fe, and Se concentration to Cd in the human kidney is the lowest in comparison to Hg and Pb. Increased kidney copper and urinary losses may be common denominators in the manifestation of renal toxicity induced by heavy metals. Factors affecting availability and loss of copper should be identified and measured. The critical kidney concentration for Cd, Pb, and MeHg should be revised in relation to essential elements.

Index Entries: Zn; Cu; Pb; Se; toxic elements, absorption of.

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INTRODUCTION

Several tragedies of mankind during the past few decades are closely associated with accidental contamination of water and food by toxic metals. Itai-itai disease owing to cadmium poisoning (*1*) and Minamata disease owing to methylmercury poisoning (*2*) are good examples illustrating the impact of metal contamination in the environment. Lead poisoning has also been reported from sources, such as drinking water, improperly glazed earthenware vessels, and illicitly distilled whisky (*3*). The environmental and toxicological problems have been discussed recently in several reviews and monographs for mercury (*2*), methylmercury (*4,5*), cadmium (*6–12*), and lead (*3,13*).

Heavy metals are known to markedly alter the metabolism and function of some essential trace elements, such as copper, zinc, iron, calcium, manganese, and selenium, by competing for ligands in the biological system. Such competition and the ligand-binding may have adverse effects on the disposition and homeostatis of essential trace elements. Transport mechanism of some of the essential elements that are involved in normal metabolic functions may be used also by some nonessential metals (*14*). In such cases, deficiency of a certain essential element may result because of interference with its absorption. Both in acute and chronic exposure, toxic metals can interact with many different cellular components, thereby interfere with normal metabolic functions, causing cellular injuries, and—in extreme cases—death of the organism. The mechanism of interaction of essential and toxic metals can be mediated through three separate ways: (a) by competition for membrane sites, (b) replacement of metals from low molecular weight protein to high molecular ones, and (c) alterations in organ distribution of metals.

Many of the interactions between zinc, copper, mercury, and cadmium can be partially explained by the binding of these metals to metallothioneins (MT). This metal binding protein may cause tissue deposition of zinc and copper ions and may also affect uptake of toxic ions in targeted organs, such as kidneys (*15*). Other carrier proteins, such as transferrin, which binds iron and zinc (*16*) and a high molecular weight plasma protein that binds copper in the early phase of copper absorption (*17*), must be considered for investigation of cadmium interaction with each of these elements. There are many reports that indicate that dietary deficiencies of some micronutrients, including mineral and trace elements, may enhance the absorption of toxic metals in experimental animals and humans. Zinc deficiency recently has been shown to result in increased cadmium in the liver, whereas iron and copper deficiencies each caused increased cadmium uptake in the kidneys (*18*). Cadmium interferes with the normal metabolism of both zinc and copper and increased intakes of cadmium in experimental animals can give rise to clinical symptoms which may, under certain conditions, be prevented by dietary supplementation of the above elements (*19*). Many of the ob-

served clinical effects of toxic metals are thought to be results of induced secondary deficiencies of essential trace elements, such as zinc, copper, and iron.

Several essential nutrients are known to decrease the accumulation and toxicity of mercury, cadmium, and lead in experimental animals. These nutritional interrelations, however, are, at present, not explained in human subjects. The toxicological investigations of heavy metals, whether experimental or clinical, must be based on a definite consideration of the nutritional status of animals and humans, especially that of the essential trace element status.

INTAKE AND HEALTH EFFECTS OF ESSENTIAL AND TOXIC ELEMENTS IN HUMANS

Dietary Intake and Absorption

Knowledge of the pathogenesis of trace element deficiencies or excesses has emerged from studies of trace element cycles in the environment (*20–23*). Evidence of human diseases emerging from the introduction of various toxic metals in the environment leads to greater appreciation of the importance of interaction among these elements, as well as with other nutrients.

For each element, there is a range of safe and adequate exposure, within which homeostatis is able to maintain optimal tissues concentration and functions. Every trace element is potentially toxic when the range of safe and adequate exposure is exceeded. A living organism has powerful mechanisms that maintain the plateau of optimal function in the biological dose-response curve throughout a wide range of dietary and environmental exposure. The specific carrier molecules of trace elements are normally less than fully saturated, and this presents a certain buffering capacity against excess, but control of absorption or excretion mechanism(s) or both is quantitatively more important (*20*). There are significant interactions between the endocrine system and trace metals in such a way that physiological and biochemical levels of trace metals may influence hormones, and conversely, hormones may influence trace metal metabolism including secretion, transport, and binding.

Gastrointestinal absorption of trace and toxic elements is known to occur in three different phases:

1. The intraluminal phase with its chemical reactions and interactions with the contents of stomach and intestines;
2. The translocation phase, i.e., diffusion or transport of the element across the cell membrane of the enterocytes; and
3. The mobilization phase, including mobilization and transport of the intracellular elements into the bloodstream or their sequestration back into intestinal lumen.

The concentration of essential and toxic elements in the body may change owing to factors such as sex, age, nutrition, dose, retention, and chemical form. Table 1 presents normal dietary intake, body concentration, and gut absorption in human subjects of essential and toxic elements. The results presented by Buchet et al. (*24*) (Table 1) suggest that about 1–2% of the daily meals analyzed had mercury and cadmium contents that exceeded the tolerable level proposed by WHO. In the case of lead, this level exceeded in 10% of the daily diets. The average daily dietary cadmium intake among the adult rural population in Japan was estimated to be 43.9 and 37.0 μg/d for males and females, respectively (*25*).

Dietary and Health Effects of Essential Elements

Zinc

Zinc is probably one of the most important and interesting inorganic elements related to health sciences (*19,21,23*). The absorption of zinc takes place mainly in the duodenum and is affected by a number of factors (*26*). Among the antagonizing substances, the major inhibitor of zinc absorption is phytate, which is present in many cereals and vegetables. Approximately 10–30% of the ingested dietary zinc is absorbed, depending upon its bioavailability. The urinary excretion of zinc in healthy adults is very low (100–900 μg Zn/d), but rises markedly in nephrosis, diabetes, porphyria, and alcoholism. The average intake of zinc in affluent countries is around 8–20 mg/d (*26*). Zinc deficiency in animals has resulted in congenital malformations, growth retardation, abnormal bone metabolism, atrophy of the testes, and deformative changes in the skin. Zinc deficiency hypogonadism, associated with dwarfism, hepatosplenomegaly, and geophagia in humans is a well-established syndrome today. Zinc may have some protective effect against the action of heavy metals (*26*). The metal also has been found to have a role in experimental and human cancer. Zinc may also be involved in the pathophysiology of liver disease (*21–23*). Acute and chronic zinc deficiency may develop during a number of diseases, including diseases that cause increased loss of protein and other substances from the body (*22*).

Iron

The physiological mechanisms behind iron absorption are still not entirely known. Iron absorption follows two different patterns depending on the source of iron, that is whether it is heme- or nonheme iron (*27*). Absorption of dietary iron takes place mainly in the duodenum. The mean intake of iron in many countries is around 12 mg/d (*26*). Only 5–15% of the iron present in the diet is absorbed under normal conditions. Biliary excretion of iron is estimated to be around 1 mg/d, and this originates mainly from the hemoglobin breakdown and most of this iron is reabsorbed. The mean urinary excretion of iron is 0.2–0.5 mg/d. A

Table 1
Daily Intake, Absorption, and Body Concentration of Some Essential and Toxic Elements[a]

Elements	Dietary intake, mg/d		Absorption, %	Body concentration, g
Essential	Recommended	Actual		Without deficiency effects
Zn	15	8–15	20–30	2.0–2.5
Cu	2–3	1.2–4.8	30	0.2–0.3
Fe	10–18	12–30	5–15	4–5
Se	0.05–0.2	0.003–0.15	60	0.005–0.007
Toxic	Permitted	Actual		Threshold for toxic effects
Cd	0.075	0.002–0.880	5	0.04
MeHg	0.030	0.001–0.497	90	0.02–0.40
Pb	0.050	0.001–1.767	5–10	0.40

[a]From Buchet et al. (1983), Sherlock et al. (1984), and Abdulla et al. (1984).

central factor in the pathogenesis of iron deficiency, particularly among the poor, is the consumption of diets based on plant products, particularly cereals and legumes. Dietary fiber, phytate, and other substances in food can substantially reduce the nutrient density of bioavailable iron (*27*). Iron deficiency anemia is very often defined according to the decrease in hemoglobin levels and is implicated in impaired physical work capacity (*29*) and poor neuropsychological function (*30*). From a nutritional point of view, iron deficiency is one of the most important public health problems. Iron status is usually judged by measuring transferrin saturation level and ferritin in serum. Values less than 10 μg/L of serum ferritin indicate very low body stores of iron (*28*).

Copper

In comparison with the amounts of iron and zinc, the copper content in the human body is about 20–50 times lower, About one-third of the total body copper is found in the liver and brain. The ingested copper is mainly absorbed from the duodenum in humans. About 10–30% of the dietary copper is absorbed (*31*). The absorption of copper is antagonized by a number of dietary components (divalent cations, phytate). The normal excretory pathway is via the bile. Only small amounts are lost in the urine (10–60 μg/d) (*32*). A recent report indicates that nearly 80% of the diets consumed by adults in most countries contain copper levels less than 1.5 mg/d (*33*). The National Academy of Sciences in the USA and WHO recommend that the dietary intake of copper should exceed 2 mg/d (*31*).

In animals, anemia, depigmentation disorders, neonatal ataxia, and cardiovascular defects are some of the conditions associated with dietary deficiency of copper (*23*). Recently, Mason (*34*) reported cases of clinical hypochromic anemia and neutropenia in humans associated with copper deficiency. Long-term treatment with zinc in humans may induce secondary deficiency of copper (*26*).

One of the important roles of copper is related to the mobilization of iron and its absorption. Several studies indicate that "environmentally relevant" concentrations of cadmium or zinc can impair utilization of copper in animals whose diets are only marginally adequate in copper and conditional copper deficiency may be induced (*21*). Antagonistic trace elements may affect the utilization of copper by reducing its solubility within the intestinal lumen or by competing with copper during its absorption or transport. The results of Klevay et al. (*35*) indicate that nutritionists should consider the copper requirement more seriously. Factors affecting the bioavailability and loss of copper during food manufacturing and processing should be identified, and the general public must be assured about the adequacy of copper intake.

Selenium

In recent years, selenium has attracted considerable attention in human health and disease. The deficiency of this element has been shown to occur in many parts of the world. Such deficiencies are associated with a number of diseases, including cardiovascular diseases, inflammatory conditions, and cancer. Selenium has long been recognized as an element of importance in liver detoxication functions also (*42,43*). Since the dietary content of selenium vary widely and may be suboptimal or deficient for animals as well as humans, it may modify the course of liver damage. Regression of selenium balance vs intake indicates that adult men require 80 μg Se/d to stay in balance, whereas women require only 57 μg Se/d (*44*). Healthy young men lose about 54 μg of Se/d via urine and feces. Recent total diet studies in the US reported levels ranging from 0.07–0.40 ppm in various food groups. Daily dietary intake of selenium in humans in most parts of the world range from 4–35 μg in infants and 60–300 μg in adults (*36,37*). Normal intakes of selenium vary considerably in different areas of the world according to environmental levels and dietary habits, from about 20 μg/d in the South Island of New Zealand, a region naturally low in selenium (*38,39*), to 5,000 μg/d in high Se regions, such as Enshi in China, during an outbreak of chronic selenosis owing to the consumption of corn with a high Se content (*40*). Many diets in different countries provide 100–200 μg Se/d (*41*). The bioavailability of selenium is also variable. Selenium from plant sources has the highest bioavailability (60% or more), whereas selenium from animal sources is less than 25% available (*45*).

A very important aspect of selenium in human nutrition is its apparent role in the prevention of malignant diseases. Selenium has been

shown to have cancer-protecting properties in animals, and there is evidence that the human cancer mortality is lower in areas rich in selenium (*46*). Selenium is now added to most animal feeds to prevent selenium deficiency diseases, such as White Muscle Disease in lambs and exsudative diathesis in chicks. In humans, selenium supplementation has been effective in preventing Keshan Disease, a cardiomyopathy affecting children and young adults in low-Se regions of China.

A conditioned nutritional deficiency of selenium may be induced experimentally by heavy metals exhibiting a high affinity for selenium. Heavy metals influence bioavailability, uptake, transport, and physiological activity of selenium and abolish its cancer-protective effects even at close to background levels of exposure (*47*). These recent developments are particularly relevant to the topics covered in the present review.

Dietary and Health Effects of Toxic Metals

Among the heavy metals arising from environmental and occupational exposure, lead, mercury, and cadmium are the most important ones. In assessing the potential impact of environmental exposure of a toxic metal, the terms "critical concentration" or "threshold" (the lowest level of exposure necessary to produce a detectable adverse effects) are often used (*48*).

Lead

The average dietary lead intake in Europe varies from 45–120 μ/d (*26,49*). Horiuchi (*50*) estimated the lead intake in Japanese diets and found values ranging from 240–320 μg in polluted areas and 136 μg in nonpolluted areas (*51*). The average level of lead found in 15 daily dietary portions of teenagers in Sweden was 44 μg (*26*). The provisional standards set by the FAO/WHO for tolerable intake of lead per week is 50 μg/kg body wt (FAO/WHO, 1972).

The effects of lead poisoning on the hemopoietic, CNS, and renal systems are well documented (*3*), but there is considerable debate about long-term effects of continued exposure to low levels of lead. Young children are particularly susceptible to the toxic effects of lead. According to many reports, the range of blood lead concentrations in excess of 300 μg/L is frequently found in children living in urban areas. The critical effect that manifests total inhibition of ALA-D in blood, and increase of FEP starts within blood lead levels between 200–300 μg/L. A trend toward anemia is noted at levels about 500 μg Pb/L blood (*13*). Chronic nephropathy induced by lead is characterized by slow development of contracted kidneys with arteriosclerotic changes, interstitial fibrosis, and glomerular atrophy. Apparently, prolonged exposure to lead levels greater than 700 μg/L is necessary to produce nephropathy. In the earliest stage of renal response to lead exposure, reversible tubular effects

may occur. These include the appearance of intranuclear inclusion bodies as a lead–protein complex rich in acidic amino acids (*3*). They have a high specific affinity for lead compared with that for Cu, Fe, Zn, or Cd, and about 90% of the lead in the kidney is associated with them. The appearance of these bodies is accompanied by aminoaciduria, glycosuria, and hyperphosphaturia (Fanconi syndrome). Lead is concentrated in the kidneys of lead-exposed mammals and causes hyperaminoaciduria, glycosuria, and hyperphosphaturia—all reflecting decreases in renal tubular reabsorptive processes (*52*). Lead poisoning may also affect the renin–angiotensin–aldosteron system. A dose of 0.1 mg Pb/kg was sufficient for rats to cause significant increase in plasma renin and the renal excretion of sodium. The threshold dose of lead is 50 μg/L in blood and 1.2 μg/g (wet wt) in kidney (*53*). This concentration is lower than that generally seen in the blood of humans (100–150 μg Pb/L). The normal concentration in human kidneys is about 0.5–0.7 μg/g (*54*).

Cadmium

The concentration of cadmium in foods can vary according to environmental cadmium exposure. Analyses of diets characteristic of several countries show that adult cadmium intake from food ranges from 4–84 μg/d (*2*). According to one report, the dietary absorption of cadmium is in the order of 25–75 μg/d (*11*). The total body burden of cadmium in humans increases with age (*55*) from very minimal levels at birth (1 μg) to an average of up to 30–40 mg by the age of 50 in nonoccupationally exposed individuals. The kidneys contain approximately one-third of the average body burden, with the highest levels localized in the renal cortex. The observed decline in kidney cadmium concentration after age 50 is attributed to the age-dependent changes in food intake and increased excretion (*56*). The average concentration of cadmium in the renal cortex is approximately double in smokers (*57–59*). The concentrations of Cd in renal cortex and the liver permit an evaluation of total body burden. The concentration of Cd in the kidney increased nearly 50-fold during the period from 1897–1939 (*60*). In the liver, it remained more or less the same. The multicompartment model used by Kjellström and Nordberg (*61*) showed that the daily intake of cadmium varies with age and calorie intake. It was calculated that at 45 years of age, a maximum average concentration of 200 μg/g in renal cortex (critical concentration) will be reached after an average daily exposure of 440 μg Cd in a 70 kg person. An average daily intake of 32 μg was estimated to result in a critical concentration above 200 μg/g in renal cortex in 0.1% of the population. The corresponding value for reaching the critical concentration in 1% of the population is about 60 μg/d. In humans exposed to environmental cadmium, a liver concentration below 30 μg/g corresponded to a renal cortex level below 200 μg/g (*62*).

The symptoms and signs after acute cadmium ingestion are nausea, vomiting, abdominal cramps, and headache. The concentration of cad-

mium in water that gives rise to vomiting is about 15 mg/L. Long-term excessive ingestion of cadmium results in kidney damage, anemia, liver disturbances, hypertension, and bone disorders (*55*). Renal tubular damage is the chronic effect attributed to environmental cadmium exposure for the nonoccupationally exposed population (*63–65*). In the European communities, a small fraction of the population with potentially high cadmium exposure—heavy smokers of cigarets and people living around cadmium-emitting sources—may be at risk of adverse health effects owing to long-term cadmium exposure (*66*). The excess mortality rate from renal diseases found in Liege and the cadmium levels in the kidney cortex of the deceased from this area were higher than that from other areas of Belgium.

Mercury

The average methylmercury intake varies from 20 μg/d in normal diets to 80 μg/d or more in heavily contaminated food (*67*). Approximately 80% of our daily intake of mercury is methylmercury, and the principal source of mercury is seafood. The intake of mercury in Sweden was found to be 3–6 μg/d (*26*). High concentrations of methylmercury in deep water predators (whale, swordfish, tuna, and halibut), in the range of 0.2–2 ppm (*68*), occur as a consequence of the diets of these animals, their slow excretion rates for methylmercury (of the order of 1000 d), and their long life spans. Persons who eat ocean fish regularly have significantly high blood mercury levels. The increased methylmercury in some fish, owing to acid precipitation and the demonstration of significant lesions at clinically nontoxic levels, suggest that the safety margin may be narrow. The health consequences arising from the consumption of contaminated fish depend on the amounts of methylmercury absorbed over long periods of time. The threshold body burden would be reached with a consumption of about 200–500 μg methylmercury daily. The allowable intake according to the Joint FAO-WHO Expert Committee on Food Additives (1972) is equivalent to a daily intake of about 30 μg methylmercury. Ingestion in the Iraq outbreak of MeHg poisoning, for example, was about 1–15 mg Hg/d over a period of about 2 mo (*69*). Lower levels of mercury may result in symptoms after a longer exposure time. The peak body burden at low exposure level was estimated to be 25–40 mg methylmercury for a 50 kg individual. A 40 mg body burden would be expected with a daily intake of ca. 900 over a 2-mo period (*70*).

Toxic exposure to methylmercury primarily results in neurological damage characterized chiefly by ataxia, sensory disturbances, and changes in mental state. The toxic activity of methylmercury manifest primarily in the sensory and motor centers of the central nervous system, probably by inhibiting the sulphhydryl groups in proteins and enzymes. A fetus has a high vulnerability toward methylmercury toxicity. Methylmercury readily crosses the placental barrier and accumulates in the developing fetus. With time, levels of methylmercury in the fetus may

exceed those of the mother (*71*). The lowest whole blood level of mercury, in which symptoms appear, is around 0.2 ppm (*72*). However, some authors suggest that symptoms may occur in susceptible individuals already around 0.1 ppm.

The basic dose–response data of Bakir et al. (*73*) is generally accepted, and the estimated threshold concentrations for parasthesia (the earliest symptom) are 0.2–0.5 ppm in blood and 50–125 μg/g in hair. Various epidemiological studies from exposed areas indicated an intake of 3–7 μg/kg/d. The first clinically important symptoms, namely ataxia, visual disorders, and dysarthia appeared in patients who had threshold levels two to fourfold higher than those who showed the symptom of parastesia alone. The blood values in these subjects were in the order of 1000–2000 μg/L or higher. This corresponds to a body burden of 80–160 mg for a 50 kg individual and an intake of 1.5–3.0 mg/d over a 2-mo period considering a half-time of 70 d (*5*).

Alkylmercuric compounds have both neuro- and nephrotoxic actions in the rat (*74–76*). Repeated exposure to methylmercury in animals provide an estimation of methylmercury concentrations in the tissues on the basis of its concentration in the blood. The tissue/blood quotients in the rats were: brain/blood, 0.12; liver/blood, 0.23, and kidney/blood, 1.17 (*77*). Chronic exposure to methylmercury produced greater nephrotoxic effects than acute intoxication (*78*). An important factor to consider in renal pathogenesis of alkylmercuric compounds is the biotransformation of organic to inorganic mercury (*77*). Mercury concentration in kidney at the level of 36.3 ± 3.9 μg/g was sufficient to cause damage to various cell types, as determined by electron microscopy (*79*).

INTERACTION OF TOXIC METALS AND ESSENTIAL ELEMENTS (ANIMAL STUDIES)

Tissues Interaction

Changes in the homeostasis of essential elements, especially zinc and copper, induced by toxic metals have been studied from the standpoint of understanding the harmful action of the metals in the organism. Disturbances in the metabolism of endogenous metals have been induced in experimental animals by administration of cadmium (*80–83*), nickel (*84,85*), silver (*84,86*), bismuth (*87*), gold (*88*), tin (*89*), molybdenum (*90*), inorganic mercury (*86,91,92*), methylmercury, ethylmercury (*77*), manganese (*93*), and lead (*94*). In general, these changes occur in tissues of experimental animals in which increases in the level of metallothionein-like proteins by toxic metals have been noted previously. The following metals have the ability to induce methallothionein: B^{3+}, Cd^{2+}, Hg^{2+}, Zn^{2+}, Ag^{+}, Cr^{3+}, Mn^{2+}, In^{3+}, Pb^{2+}, Sn^{4+}, Co^{2+}, Fe^{2+}, Au^{+} (*95*).

The metallothionein induced by various metals doubtlessly contains zinc or copper together with toxic metals. Studies of these proteins revealed that they differ in the content of endogenous metals depending on the organ in which the stimulation takes place. In metallothionein-like protein of the kidneys, copper dominates as endogenous metal (*77,87*), whereas in the liver it is zinc (*96*).

At low dietary zinc concentrations, a larger portion is taken up by intestinal cell and is directly transferred to the plasma. At higher concentrations, increasing levels of metallothioneins in the intestinal cells trap a larger portion of zinc taken up by these cells and thereby decreases the net zinc transfer to the plasma (*97*). On this basis, a feedback mechanism regulating zinc absorption has been postulated: increasing concentrations of zinc in the plasma stimulate increased MT synthesis in the intestinal cells, which leads to a greater trapping of absorbed zinc and eventually loss by desquamation and a relative decrease of the nutritional supply to the organism. As the plasma zinc concentration declines, the stimulus for MT synthesis diminishes, and the portion of absorbed Zn available for transport into the circulation is correspondingly increased. Mechanism of this nature may be one of the predominating regulators of homeostatis for iron, zinc, copper, and possibly for other elements for which the regulation by urinary excretion is relatively insignificant.

Cadmium

One of the proposed roles of MT is its function as a carrier protein for metals such as Cd, Zn, and Cu, especially from the liver to kidneys. Cadmium can displace hepatic zinc from Zn-thionein and this interaction plays the protective role of Zn against several toxic effects of Cd (*98*). Although the biological half-time of cadmium is extremely long (10–20 yr) and cadmium is present as bound to metallothionein, the biological half-time of the apoprotein, thionein, is as short as those of usual proteins (6–9 wk) (*99*). This fact suggests that the toxicity of cadmium may be owing to those metal ions that are not bound to metallothionein.

The chemical forms of Cd in plasma are the main controlling factors that determine its distribution either to the liver or kidney. Cadmium bound to the high molecular weight plasma proteins is mostly trapped by the liver, whereas the metal bound to lower molecular weight components is either selectively transferred to and taken up by the kidney or directly excreted in urine. Zinc and cadmium in MT coming out from the liver are partly replaced by Cu in plasma.

Both cadmium and zinc can directly inhibit copper uptake by intestinal cells and also lead to entrapment of absorbed copper in the intestinal cells by inducing metallothioneins (*21*), thus reducing hepatic levels of Cu. The accumulation of zinc by the liver and diminished plasma concentration confirm the suggestion that, in the presence of cadmium, the synthesis of MT is increased that binds both the metals. The reduction in renal metallothionein during zinc deficiency could manifest early onset

and enhance the nephrotoxic effect of cadmium. Anemia is one of the most sensitive parameters of oral Cd intoxication (*100,101*). After oral cadmium uptake, there is usually a reduction in hemoglobin and hematocrit, whereas cadmium inhalation with comparable Cd organ levels, no anemia is observed. Even a small dose of oral cadmium administration may cause a decrease in the iron concentration in the liver of rats (*102*).

Cadmium can compete directly with iron for intestinal absorption, and it has further been suggested that similar to the action of zinc, cadmium may inhibit the uptake and release of iron through binding to ferritin (*80*). Such a mechanism would be expected to lower the plasma concentration of iron quickly, but the loss of iron from hepatic stores would take longer intervals. The significance of transferrin for intestinal iron absorption and high molecular-weight plasma proteins that binds copper in the early phases of copper absorption may provide additional pathways for Cd interaction with each of these elements. It seems likely that the competition between Cd and Fe in the gastrointestinal mucosa mainly contributes to the decrease of iron absorption. Iron concentration in the organs may differ when cadmium is administered by different routes (*103*). When cadmium is given orally, the decrease of iron in serum may be owing to the depression of Fe absorption from the gastrointestinal tract through the competition between Cd and Fe. This is supported by the low concentration of intestinal iron (Table 2). Under such circumstances, the same competition may take place in the kidneys. It seems that the competition between cadmium and copper in this organ is significant because the concentration of copper is lower after a low exposure to cadmium. The antagonistic effects of dietary cadmium on Cu is probably of greater significance than that of Zn. Increasing dietary cadmium concentrations significantly decrease liver Cu contents. The ingestion of dietary Cd after birth is a major factor in reducing liver Cu deposition (*107*). Iron and copper metabolism are closely interrelated, and the effect of cadmium on one may easily involve interaction with the other. Cadmium ingestion resulted in alterations of the concentrations of copper and iron in serum and kidneys even when the diets contained high levels of these essential elements.

Dietary cadmium administered for more than 10 wk (*80,81,108*) or for a year or more (*109*) was deposited in the kidneys in a dose–dependent manner, from a dose of 4 μg Cd/g (*80*) up to 277 μg Cd/g (*109*). An increase in the level of copper was noted even at the lowest cadmium level in this organ. In the liver, the cadmium concentration amounted to 6 μg Cd/g and 88 μg Cd/g, respectively, at 10 wk and 1 yr after cadmium administration. In the liver, as in the kidneys, no clear-cut differences of the copper level were found, but a significant increase in the level of endogenous zinc was detected in this organ, even at the lowest cadmium levels, compared with the control group. Subcutaneous injection of cadmium increased the Cd level in the kidneys up to 11.4 μg Cd/g and caused a rise in the content of endogenous copper in the

Table 2
Concentrations of Trace Elements in Some Selected Rat Tissues and Body Fluids (μg/g)[a]

Elements	Kidney	Liver	Intestines	Whole Blood	Urine, μg/24h/rat
Cu	4.0 ± 0.3 11.4 ± 1.7	4.6 ± 0.3 6.4 ± 1.2	0.8 ± 0.1 2.1 ± 1.8	1.4 ± 0.2	12.7 ± 0.9
Zn	20.5 ± 2.0 28.6 ± 2.4	30.7 ± 2.5 44.6 ± 3.3	32.2 ± 2.6	6.1 ± 1.0	10.3 ± 1.4
Fe	49.4 ± 5.6 87.4 ± 3.9	91.8 ± 20.7 220.0 ± 10.6	17.7 ± 1.5	291.9 ± 50.5	

[a]From Sugarware et al. (1984) (*106*), Solecki et al. (1984) (*104*), Chmielnicka et al. (1985) (*105*), and Komsta—Szumska and Czuba (1986).

exposed rats (*110,111*). Also, in the liver of the rats exposed to cadmium at a conc. of 38.4 and 300 μg Cd/g, respectively, zinc induction was higher than that found by Sato and Nagai (*112*) and Bonner et al. (*113*). On the other hand, Kotsanis and Klassen (*114*) and Wessenberg et al. (*115*) observed a decrease in the Cu and Zn levels in the kidneys of rats subjected to a prolonged exposure to Cd. The copper concentration that continued to increase with the accumulation of cadmium in the rat kidney suddenly dropped to lower levels after the damage when compared with controls (*124*). The damage usually occurs after a cadmium accumulation of 60 μg/g in the kidney. At this cadmium concentration, a clear evidence of tubulo-interstitial nephrititis appeared in the experimental animals (*116*). Moreover, slight changes were first noted when Cd concentration in the kidney was 6–8 μg Cd/g (*116,117*). These observations were made in the experimental animals at a renal concentration of cadmium, which is of the same order as that found in humans who are heavy cigaret smokers with levels well below the accepted critical organ concentration. Decreased structural integrity of parenchymal cells, was evident at a hepatic concentration of 60 μg Cd/g (*118*), and it supports the hypothesis of Colucci et al. (*119*) that the onset of liver injury starts at a Cd concentration of 40 μg/g.

On the basis of these data, it may be concluded that disturbances in the metabolism of endogenous zinc in the liver and endogenous copper in the kidneys of rats already occur when the concentration of cadmium reaches about 20 μg Cd/g kidney tissue. Higher concentrations of this metal may lead to a plateau of this biological effect or even its diminuition.

Mercury

Similar phenomena with regard to copper metabolism was noted in the case of exposure to alkylmercurials (*77*). The increase in copper appeared when the inorganic mercury liberated from the alkylmercurials

exceeded 10 μg/g and reached a plateau of about 40 μg/Hg/g kidney. The levels of metallothionein-like proteins in rat kidney were dependent on the concentration of inorganic mercury liberated from biotransformation of alkylmercurials. A statistically significant increase in the levels of metallothionein-like proteins and endogenous copper was found in the kidneys of rats intoxicated with methyl- and ethylmercury compounds (*77*). Changes in the distribution of the essential elements, iron, copper, zinc, and calcium was observed in pregnant and fetal rats exposed to inorganic, methyl- and ethylmercuric chloride (*91,105,120*).

Lead

Significant decreases of copper in the liver and iron in the whole blood in rats were also observed when concentrations of lead were 4.63 ± 1.24 and 186 ± 108 Pb μg/g, respectively (*94*). The results of Wessenberg et al. (*115*) showed positive, as well as negative correlation between Pb, Zn, and Cu in the tissues.

The increased renal Cu found after the combined ingestion of lead and cadmium may have been caused by lead alone or lead and cadmium acting together. Intestinal metallothionein also binds lead. On the other hand, lead was retained in the kidney, but not in the liver of rats fed with diets containing lead (*121*). Lead ingestion can reduce the nutritional efficiency of zinc and copper by causing a decrease in the absorption of these elements (*82,98*). Interactions between lead, zinc, and copper may manifest by interfering with iron metabolism and may effect hematopoeisis. An interaction of potential significance in human nutrition is the interaction between zinc and iron. Iron deficiency causes an enhanced intestinal affinity not only for iron, but also for other ions, including zinc (*122*). The fate of copper in lead intoxication is less well-established than that of zinc, but recent work by Petering (*123*) indicates that the lead-induced reduction of kidney zinc was greatly minimized by increasing the dietary intake of copper in rats under experimental conditions, a fact that suggests a definite Zn–Cu–Pb interaction. Increased concentration of kidney copper may be a common manifestation of heavy metal induced renal toxicity. Bogden et al. (*91*) suggest that the classical nephrotoxic effects of inorganic mercury may be, in part, owing to the associated elevated copper levels. If other heavy metals besides Cd and Hg also produced the increasing of copper in the kidney, this would suggest a common mechanism of nephrotoxicity.

Excretion of Toxic and Essential Elements in the Urine

Recent animal experiments have demonstrated that cadmium exposure causes an increase of the urinary excretion of some essential metals, such as copper, zinc, and iron (*111,114,117*). The release of enzymes from the kidney into the urine reflects the course of Cd-induced renal damage, occurs at an earlier stage than some other indications of dysfunction, and

also correlates with loss of Zn, Cu, and Fe in the urine and with the progress of kidney damage (*108*). Cadmium is bound to copper-rich metallothionein before the damage, while it is bound to MT containing smaller amounts of other metals (Zn and Cu), especially Cu, after the damage (*124*). A persistent damage can be observed when the concentration of Cd reaches a maximum level and is maintained at a plateau concentration. The persistent renal damage may occur after the changes in the distribution of Cd, Zn, and Cu in the kidney.

The urinary excretion of Cd, Zn, and Cu can be partly explained by the urinary excretion of metallothionein, as reported after repeated injections of Cd in animals. However, the larger amounts of the three metals excreted, compared to the corresponding control levels, cannot be explained simply by the three metals bound to metallothionein, because the relative amounts of Zn and Cu bound to MT were lower than those of Cd in the liver and kidneys (*124*). The increase of urinary Cd, Zn, and Cu after dietary Cd in the basal diet is also documented. The origin of urinary MT may depend on the extent of Cd accumulation in the kidneys and also on the renal damage (reabsorption rate). The reabsorbed MT is degraded and the Cd liberated from the degraded MT is sequestrated as the copper-rich MT within the native biosynthesis capacity. The urinary MT contains copper in high concentrations irrespective of its origin and can be easily oxidized both by divalent copper and dissolved oxygen. Urinary MT levels were elevated in response not only to Cd, but also by Hg, Cu, and Zn. Mercury had the most profound effect at equimolar doses (*125*).

Inorganic mercury is mainly accumulated in the kidney and has been shown to induce MT synthesis (*126*). The marked increase in kidney Cu after Hg treatment reported by Lee (*125*) is consistent with the observations of Chmielnicka et al. (*77,92*). Since inorganic Hg at a dose of 1 mg/kg causes renal tubular damage (*127*), resulting in urinary excretion of the metal owing to cell sloughing, this may also be a possible mechanism of increased excretion of MT in urine of Hg-treated animals and is presumably owing to the association of Cu with the renal MT. The amounts of copper and zinc excreted daily in the Hg-treated animals were about three to fourfold greater than in the corresponding control groups (*92*). The increase in the urinary levels of these metals is a more sensitive indicator of acute $HgCl_2$ nephrotoxicity than the activity of Zn-dependent enzymes (*128*).

PREVENTIVE EFFECT OF DIETARY SELENIUM TO TOXIC METALS

Methylmercury and Selenium

Selenium administered to Se-deficient mice ameliorated both the neurotoxic effects and nephrotoxic action of MeHg (*78*). The changes in the retention and distribution of selenium, administered jointly with

mercury, depend upon the chemical form of the compounds, the administered dose, and the experimental interval. Selenium reduced the toxicity of all three mercury compounds (inorganic, aryl, and methyl Hg).

Changes in the distribution of mercury by selenium in rat tissues are apparently owing to the binding of selenium to inorganic mercury liberated from alkylmercurials by biotransformation. Mercury–selenium complexes are formed owing to the interaction between mercury and selenium. This phenomenon is expressed especially well in the case of ethylmercuric chloride owing to the high efficiency of biotransformation of these compounds to inorganic mercury in vivo (*77*).

On the other hand, at low selenium concentrations in the kidneys with respect to high concentrations of inorganic mercury, an increase in the concentration of mercury in this organ was observed. A decrease in the concentration of mercury in the kidneys occurs only at high levels of selenium (*77*). A slight excess of this element did not change the mercury content of the kidneys, whereas an equimolar dose, sufficient to induce redistribution of mercury in the case of exposure to an inorganic mercury compound, not only did not decrease, but even increased the mercury concentration in this organ (*77*). A common association between the metabolism of selenium and methylmercury is associated with the thiol-containing peptide glutathione (*129,130*) and the transport enzyme, γ-glutamyltranspeptidase. Both these compounds are influenced by methylmercury, and the enzyme may be useful as a predictive indicator of methylmercury toxicity in animals (*131*). In the presence of selenium, there are also decreases in the concentration of metallothionein-like proteins and endogenous copper, probably owing to the binding of selenium to inorganic mercury liberated and probably also to other native metals (*77*).

Selenium diminishes the affinity of inorganic mercury for the kidney and reduces the level of the metal bound to renal metallothionein (*126*). Because of this interaction, induction of metallothionein by mercury is decreased in the kidney and, as a consequence, the amount of metallothionein-bound Zn and Cu also is diminished (*92*). Sodium selenite prevents the increase of endogenous copper in the urine of rats, which may be owing to a decrease in the kidney concentration of mercury.

Very little is known about the exact nature of mercury and selenium complexes in various tissues and the role they play in bioaccumulation and mercury detoxification in animals and seafood. There has been no reported evidence of possible mercury–selenium complexes in edible seafoods. Dietary levels of selenium of the same order of magnitude as the nutritional requirement are highly effective in reducing the toxicity of methylmercury, a toxicant accumulated in fish, and this interaction is of great practical importance. The levels of selenium found in many marine fish are usually high and since the main source of methylmercury in the human diet is through the consumption of seafish, the corresponding

high level of selenium may protect against mercury toxicity. In most fish samples, 53 to 94% of the total mercury content is present as methylmercury, being notably higher in freshwater species (*132*). In all samples, a significant part of the total selenium content (4–47%) is present as selenate (Se VI). Tissue selenium levels do not correlate with corresponding mercury levels.

Cadmium and Selenium

The protective effect of selenium against cadmium-induced lethality, testicular necrosis, and other toxic effects have been studied in experimental animals when acute single doses of Se and Cd were administered intraperitoneally (*133*). The mechanism by which selenium protects against the acute toxicity of Cd, following the parenteral administration of equimolar amounts of these two elements, has been shown to involve a redistribution of Cd in tissue soluble fractions, resulting in more cadmium being bound to high molecular weight proteins than to metallothionein (*100,134,135*). The redistribution of Cd in red blood cells and plasma is associated with the formation of a specific Cd–Se complex that is bound to high molecular weight proteins. The formation of Cd–Se protein complexes allow an orderly transfer of Cd to MT since more of this protein is synthesized and the Cd–Se protein complex undergoes degradation (*136*).

It is well known that kidney damage owing to cadmium exposure is closely related to the induction of MT synthesis and the concurrent retention of Cu and Zn that is increased with the progressive accumulation of Cd in the renal tissue. Administration of Se (ip) concurrently with Cd (sc) significantly reduced the cadmium-induced enzymuria, proteinuria, and elevation of serum enzymes. The nephrotoxicity and hetapatoxicity of cadmium could be reduced immediately following selenium administration (*137*). The increase in the uptake of renal Cu and renal and hepatic Zn owing to Cd administration could also be prevented by selenium. However, there is little information about the interactions between dietary cadmium and nutritionally adequate levels of selenium. Supplementary cadmium in 0.3 ppm depressed weight gain in rats and food consumption (*102*). At the same time, a hepatic concentration of cadmium only 2.1 μg Cd/g resulted in increased zinc and decreased iron concentration that were progressed in a linear fashion with increased cadmium intake. Hepatic copper concentration tended to decrease. Consequently, depressed hemoglobin levels became worse by the relatively low intake of Cu. Dietary selenium (0.1 or 1.0 ppm) did not affect concentrations of cadmium, zinc, iron, or copper in liver. Selenium may compete with cadmium for binding with the functional biological ligands of the target tissue sites. Interactions between nontoxic levels of dietary selenium and relatively high levels of dietary cadmium apparently re-

sulted in an antagonism of selenium metabolism by cadmium in some systems and partial amelioration of cadmium toxicity by selenium in other systems. Either directly or indirectly, cadmium might impair the selenium absorption (*138*), alter selenium utilization, or both. Nonetheless, only minor effects of cadmium were seen in the other parameters in both Se-supplemented and Se-deficients animals (*139*).

Dietary cadmium depresses tissue retention of added inorganic Se, probably by interfering with absorption. Cadmium may either impair selenium absorption or alter selenium utilization. Cadmium may stimulate plasma GSH-Px activity when the diet is adequate in Se. An excess of selenium may result in two significant interactions. In animals, it may prevent the increase in liver iron normally associated with Cu deficiency, and it can cause a reduction in liver Zn. It is thought that the increase in liver Fe in Cu-deficient rats is a direct result of the failure to immobilize absorbed Fe for hemoglobin synthesis. Selenium reduces the liver iron, but has no effect on hemoglobin synthesis and, thus, suggests that Se may either reduce Fe absorption or facilitate its excretion from the liver. In turn, zinc reduces the toxicity, but also the anticarcinogenic effects of selenium, as was first demonstrated by Schrauzer et al. (*46*) and more recently by Eybl et al. (*140*).

Previously, a clear-cut interaction between exogenous Se, Zn, and endogenous Cu in rats has been demonstrated (*141,142,143*), as well as between exogenous cadmium and selenium and endogenous zinc and copper (*83*). It should be stressed, however, that there are differences in the interactions between zinc and selenium and mercury, cadmium, and selenium (*77*).

CONCENTRATION OF ESSENTIAL ELEMENTS AND TOXIC METALS IN HUMAN TISSUES AND BODY FLUIDS

The elemental composition of body fluids and tissues is indicative of the nutritional and pathological status of humans. Concentrations of essential elements and toxic metals in human tissues and organs, as well as in foods, have been studied by many authors (*144–155*). Chronic oral toxicity of cadmium, mercury, and lead may lead to alterations of zinc, copper, selenium, and iron nutrition and metabolism. This is an important concept since it brings into focus the interplay between the level of exposure and body or organ burden on one hand, and nutritional status as a host defense mechanism on the other.

Table 3 shows the values (minimum and maximum) for the concentration of essential elements and toxic metals in some selected adult human tissues and body fluids from several countries. The values determined by Subramanien et al. (*154*) for the same major, minor, and trace elements in 143 autopsied kidney and liver form two Ontario commu-

Table 3
Concentrations of Trace Elements and Toxic Metals
in Some Selected Adult Human Tissues and Body Fluids[a]

Elements	Whole blood, μg/L	Liver, mg/kg	Hair, mg/kg	Urine, μg/L	Kidney,[b] mg/kg	Milk, μg/L
Cu	0.82 ± 0.14 1.30 ± 0.60	3.2 ± 1.4 9.9 ± 1.6	10.4 ± 2.7 39.0 ± 22.0	12 ± 7.5 59 ± 23	1.0–5.1 (2.4)	197 ± 9.3 751 ± 407
Zn	4.40 ± 0.96 8.50 ± 0.10	44.5 ± 13.1 70.0 ± 28.0	124 ± 38.0 200 ± 50.0	361 ± 228 524 ± 185	16–160 (45)	780 7200 ± 4300
Fe	339 ± 23 522 ± 49	120 ± 83 293 ± 143	21 ± 27.0 296 ± 196	1.2 ± 6.44 145 ± 450	36–213 (83)	592 ± 196 1500 ± 400
Se	21 ± 1.0 180 ± 40	0.25 ± 0.05 0.70 ± 0.23	0.30 ± 0.07 3.7 ± 2.3	13 ± 1.5 125 ± 76	0.2–2.3 (0.83)	11.0 ± 2.4 34.0 ± 9.2
Cd	0.3 ± 0.3 7.0 ± 3.1	0.30 ± 0.06 4.1 ± 1.6	0.38 ± 0.28 2.43 ± 0.55	0.64 4.7 ± 4.4	5.1–109 (31)	0.66 ± 1 4.6 ± 5.0
Pb	65 ± 20 269 ± 77	0.41 ± 0.21 2.30 ± 0.06	4.2 ± 2.4 52.0 ± 12.5	10 ± 6.5 18.7 ± 8.0	0.1 ± 0.9 (0.1)	6.50 ± 7.0 26 ± 11
Hg	1.0 ± 0.12 59 ± 26	0.083 ± 0.023 0.410 ± 0.310	0.63 ± 0.26 12.2 ± 1.8	0.1 ± 0.1 1.3 ± 0.8	0.01 ± 1.92 (0.17)	0.2 ± 0.1 13 ± 3.5

[a]From Iyengar (1985).
[b]From Subramanian et al. (1985).

nities were in agreement with the data of Iyengar et al. (*155*) and some other recent studies (*156–159*) for the liver, medulla, and the cortex.

Table 4 presents the comparison of human kidney cortex cadmium concentration in a recent study from various countries. There is a tendency toward higher values for smokers than nonsmokers. Average cadmium concentrations in renal cortex among the Japanese are twice those of US residents and three times those of Sweden (*58*). The essential elements Cu, Fe, Se, and Zn are preferentially accumulated in the liver, whereas the toxic metals Cd and Hg found their way to the kidney cortex and medulla. The concentration of Cd in the cortex was almost twice that of medulla, whereas the Zn level in the medulla was roughly 73% of that in the cortex (*154*).

The concentrations of copper in the liver are several times higher than those in the renal cortex. There is not much difference in the zinc concentrations in the liver and renal cortex, but the cadmium concentrations in the renal cortex are almost 10 times higher than those in the liver. The ratio of Cd/Zn in the renal cortex increases according to age up to 40–49 yr and decreases afterwards (*144*). The critical concentration of Cd in the human renal cortex is a very important parameter for calculating the biological half-time and absorption rate. From such data, it may be possible to set the acceptable daily intake from food, as well as the threshold limit values in the air.

Figure 1 shows the average values of the concentrations of essential elements (iron, zinc, copper, and selenium) and toxic metals (mercury, cadmium, and lead) in the kidney, liver, and whole blood (μmol/kg). It is especially interesting to note that selenium and copper show a lower level in the kidney than cadmium and it is not much higher than mercury and lead. It is also important to note that the copper concentrations in the renal cortex were lower than cadmium in human populations.

Copper indicates a different pattern from other metals. It decreases slightly with age in the liver and kidney, whereas the Cd, Zn, and Pb increases (*144,151*). This indicates the possible depression of Cu absorption owing to the high dietary intake of cadmium, lead, and perhaps mercury. Cadmium also causes an increase in the excretion of copper in urine, which is attributable to renal tubular damage (*63–65*).

In liver, selenium concentrations are lower than lead and cadmium, and only in whole blood is the concentration of this essential element higher than the concentrations of toxic metals. The overall ratio of the copper, zinc, iron, and selenium concentrations to cadmium in the kidney is lowest in comparison to mercury and lead (Table 5).

All possible ratios of mercury and lead in liver and kidney to essential elements show very different patterns. The selenium and copper ratio, however, to toxic metals in the renal cortex and liver is about 10 or more times lower than the zinc or iron ratio. The relationship among metals and distribution in organs varies markedly. This phenomenon is caused not only by the affinity of a single metal for a specific organ, but

Table 4
Cadmium Concentrations in the Kidney Cortex of Humans

Cadmium μg/g kidney cortex		Authors	Year	Ref.
22	age, 50	Elinder et al.	1976	*160*
16.8	age, 50	Miller et al.	1976	*161*
203.0	age, 40–49	Tsuchiya et al.	1978	*144*
57–137	Itai-itai patients	Nogawa et al.	1981[a]	*65*
64.8	smokers	Iwao et al.	1983	*151*
45.5	nonsmokers	Iwao et al.	1983	*151*
17.8	males	Scott et al.	1983	*150*
18.4	females	Scott et al.	1983	*150*
31.1	age, 50	Subramanian et al.	1985	*154*
16.1–18.1	age, 30–59	Pandya et al.	1985	*153*
37.8–100	age, 50–59	Nogawa et al.	1986	*62*

[a]Total proteinuria was documented by Nogawa, 1981.

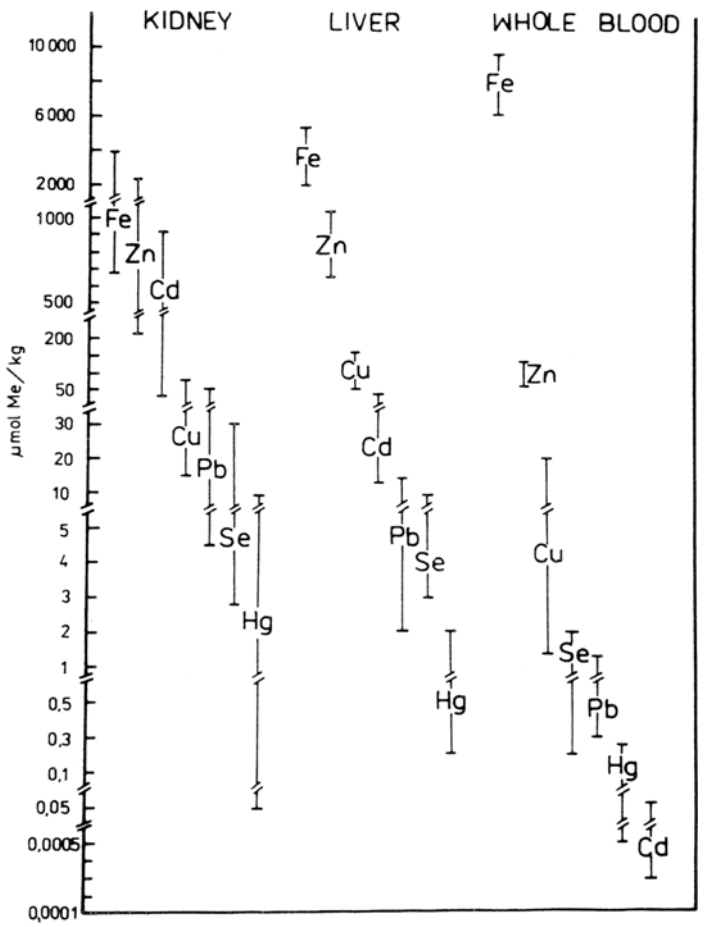

Fig. 1.

Table 5
The Ratio of Toxic Metals to Essential Elements in the Kidney and Liver of Humans

Ratio/tissues					
Kidney			Liver		
Cu/Cd, 0.08	Cu/Hg, 14	Cu/Pb, 24	Cu/Cd, 2.2	Cu/Hg, 21	Cu/Pb, 4.0
Zn/Cd, 1.40	Zn/Hg, 260	Zn/Pb, 450	Zn/Cd, 17	Zn/Hg, 170	Zn/Pb, 30
Fe/Cd, 2.70	Fe/Hg, 488	Fe/Pb, 830	Fe/Cd, 68	Fe/Hg, 732	Fe/Pb, 128
Se/Cd, 0.02	Se/Hg, 5.0	Se/Pb, 0.83	Se/Cd, 0.1	Se/Hg, 1.7	Se/Pb, 0.3

also by interactions among metals and elements. This suggests that different metabolism in human organs results in varied excretion in the urine and feces.

EXCRETION OF ESSENTIAL ELEMENTS IN THE URINE

The renal damage has been reported widely in people living in Cd-polluted areas in various parts of the world. The various biological indicators for cadmium exposure and toxicity were critically reviewed recently (*9,11,65*). The estimation of urinary Cd may not be a sensitive indicator for environmental exposure to Cd, and other parameters should also be studied. The results reported by Tohyama et al. (*63*) and Nogawa et al. (*62,64,65*) revealed the relationships between the concentrations of metallothionein in urine and those of other nonspecific urinary indices of renal dysfunction, i.e., total protein, glucose, β_2-microglobulin, retinal-binding protein, α-aminonitrogen, and proline of women living in cadium-polluted areas in Japan. The urinary MT had a significant relationship not only with urinary Cd, but also with urinary Cu. The result suggests that the elevated excretion of MT is not only an index of excessive Cd exposure, but also of renal dysfunction caused by chronic exposure to the metal.

These findings may help in the elucidation of the mechanism of the increased urinary Cu excretion owing to Cd exposure. The increased urinary excretion for copper may reflect the increased urinary excretion of Cu-binding MT caused by renal damage owing to Cd exposure.

Urinary cadmium showed significant correlations with Cu and Zn in workers who had considerable exposure to cadmium oxide fumes (*162*). In addition, a positive correlation was observed between urinary β_2-microglobulin and Cu excretion, whereas a negative correlation was found between urinary β_2-microglobulin and Zn excretion.

Mitane et al. (*163*) suggested that once MT that binds mainly Cd and Zn is liberated from liver, kidney, and other tissues into the bloodstream,

Cu will be a predominant metal in terms of metal composition in MT molecules. When renal tubular dysfunction occurs owing to Cd exposure, urinary excretion of Cu-rich MT will be increased resulting in elevated excretion of urinary Cu. More than 30% of both urinary Cd and Cu were bound to MT, and this protein is so susceptible to oxidation that metals bound to MT can be released from it and distributed in high or low molecular weight fractions in the urine. Although it is clear that cadmium-induced renal dysfunction can occur following sufficient exposure to the metal, neither the frequency nor the severity of the risk of environmental exposure is well known. The disturbances in the metabolism of the essential metals (Cu, Zn, and Fe) and increased urinary excretion of these in humans are sensitive indicators of excessive cadmium exposure in the general population although it may not be a specific effect of Cd exposure, but also of other heavy metals, such as mercury compounds and lead.

CONCLUSIONS

The gastrointestinal tract may play a crucial role in either promoting or preventing heavy metal toxicity (MeHg, Pb, and Cd) from dietary sources.

Chronic toxicity owing to gastrointestinal exposure to Pb, Cd, and methylmercury may be modified through utilization of common metabolic pathways. These metals exert toxic effects on hematopoietic and nervous systems in addition to causing lesions in the liver and kidneys.

Adequate essential metal nutrition can protect against the dietary induced toxicity of heavy metals and more attention to their preventive action against toxic metals is urgently indicated. It is very important to collect more detailed data about those nutritional interactions that provide protection against toxic metals.

The disturbances in the metabolism of the essential metals (Cu, Zn, Fe, and Se) in humans and the changes in the urinary excretion of these metals might be sensitive indicators for toxic metals exposure in the general population. The increase in the kidney Cu and Zn may be a general metabolic response to heavy metal-induced kidney damage.

Most toxic metals are excreted in the urine. Studies should be carried out to identify the metal binding components in the urine and the concentration of essential elements, such as zinc and copper.

The kidney is the appropriate tissue to study as the critical organ for chronic exposure to toxic metals. The critical kidney concentration for cadmium, lead, and mercury should be revised.

The urinary copper level is related to the tissue cadmium and the elevation of copper may be a good indicator of impaired renal function. This occurs when the concentration of cadmium in the kidney is above 50 μg Cd/g tissue in humans and 10–20 μg Cd/g in animals.

Patients with renal diseases are zinc deficient. Hypercupremia, on the other hand, is present in patients with renal disease and in people who are environmentally and occupationally exposed to cadmium. Zinc supplementation improves clinical and biochemical parameters of Zn deficiency in the patients. The cause and clinical significance of hypercupremia in patients with renal disease remains to be established.

Iron deficiency may markedly increase the proportion of absorbed metals deposited in the kidneys, and the body iron status may modulate the effects of chronic metal toxicity in the kidney. People with low iron reserves, such as women of reproductive age, might be at greater risk of developing mercury, cadmium, and lead toxicity than those who are adequate in iron.

The critical concentration in renal cortex of about 200 μg/g (ca. 2000 μmol/kg ww) should be revised. The present margin of safety regarding the risk for renal effects is small. In addition to dietary exposure, smoking is an additional source of heavy metal intake, such as cadmium.

The well-known interaction of selenium with heavy metals may decrease the bioavailability of selenium in certain foods. The nutritional bioavailability of different Se compounds must be considered on an individual basis, and the characteristics of the test population should be taken into consideration.

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