Tissue Trace Element Shifts by Acute and Chronic Exposure to Chemicals, and Its Prevention

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SUMMARY

1) Tissue trace elements were influenced by heavy metal exposure.
2) Tissue trace element shifts were related to the mechanism of health effects of metals.
3) Supplementation of trace element alleviated health effects of metals, while their element deficiency aggravated the health effects.
4) Tissue trace elements were shifted by organic solvent exposure or stress as well.
5) Aging is generally accompanied with trace element insufficiencies, which aggravated health effects of environmental or occupational contaminants.
6) It is recommended, therefore, to take diet supplemented with trace elements, especially for aged people.

INTRODUCTION

Recent progress of analytical instruments have enabled us to determine many elements in biological specimens in a short time at a low detection limit.

Multi-element analysis revealed that some heavy metal exposures elevated or depressed plasma, urine and tissue zinc or copper levels. The phenomena is called "tissue trace element shift".

We have observed that helath effects of heavy metals were associated with tissue trace element shift[1,2]. And, we have ventured a hypothesis that the mechanism of health effects of heavy metals may be associated with tissue trace element shift, and that insufficiency or deficiency of trace elements may aggravate health effects of heavy metals, or that supplementation of trace elements may alleviate health effects of heavy metals.

If the hypothesis is true, improved diet may alleviated health effects of occupational and environmental pollutants.

1. Tissue trace element shift by chronic exposure to heavy metls, and its biological significance

First of all, we shall discuss tissue element shifts by chronic exposure to heavy metals, and its biological significance.

1) Lead[1,2]

Nine male rabbits of Japanese white strain, weighing 3 kg, were given intravenous administrations of lead acetate at a dose of 2 mg/kg body weight 3 times a week. Lead decreased plasma zinc and alkaline phosphatase in 2 weeks, and induced severe zinc deficient acrodermatitis in 7–10 weeks

(Fig. 1). Acrodermatitis recovered in 3 weeks by oral supplementations of zinc sulfate at a dose of 50 mg/day.

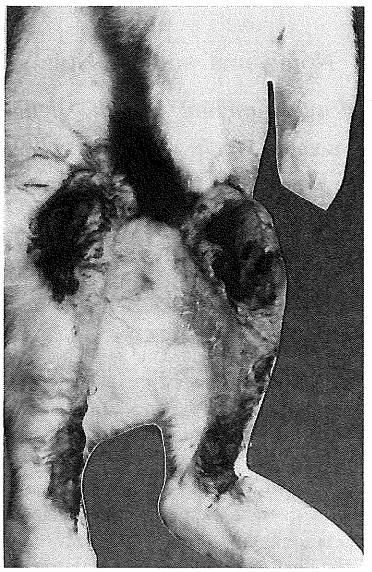

Fig. 1. Lead-induced zinc deficient acrodermatitis in a rabbit. See details in the text.

Lead may have induced zinc deficient acrodermatitis according to the following mechanism: a huge amount of hepatic zinc is necessary to produce delta-aminolaevulinate dehydratase, zinc dependent enzyme. Most of the enzyme were inactivated by binding with lead. Zinc was, therefore, supplied from the skin, the main deposit, to the liver, where zinc was utilized as materials of holo-protein, through plasma.

It may be necessary for lead workers to take more zinc in daily diet to prevent lead-induced zinc deficient acrodermatitis or related diseases.

For studying the dose-effect relationships, 24 male rabbits of another group were given intravenous administration of lead acetate at a dose of 0, 0.03, 0.1, 0.3 or 1.0 mg/kg body weight 3 times a week for 18 weeks, and 15 trace elements in the liver and the kidneys were analysed by atomic absorption spectrophotometry and induced-coupled plasma emission spectrophotometry. Dose-dependent trace element shifts observed were elevated hepatic zinc, copper, calcium, magnesium and lead, elevated renal cobalt and lead as well as decreased renal copper and aluminum as indicated in Fig. 2.

2) Cadmium[3,4,5]

Cadmium has been a heavy metal to pollute the general environment in Japan.

Twenty-four male rabbits were given subcutaneous injections of cadmium chloride at a dose of 0 or 0.5 mg/kg body weight 6 times a week for 21 weeks. Hepatic and renal copper and zinc were elevated 1.5–5 times in the 0.5 mg/kg group but in a dose-effect relationship, and then decreased below normal level. Health effects of cadmium appeared followed by the decreased tissue copper and zinc. Cadmium health effects may therefore be predicted by tissue trace element shifts.

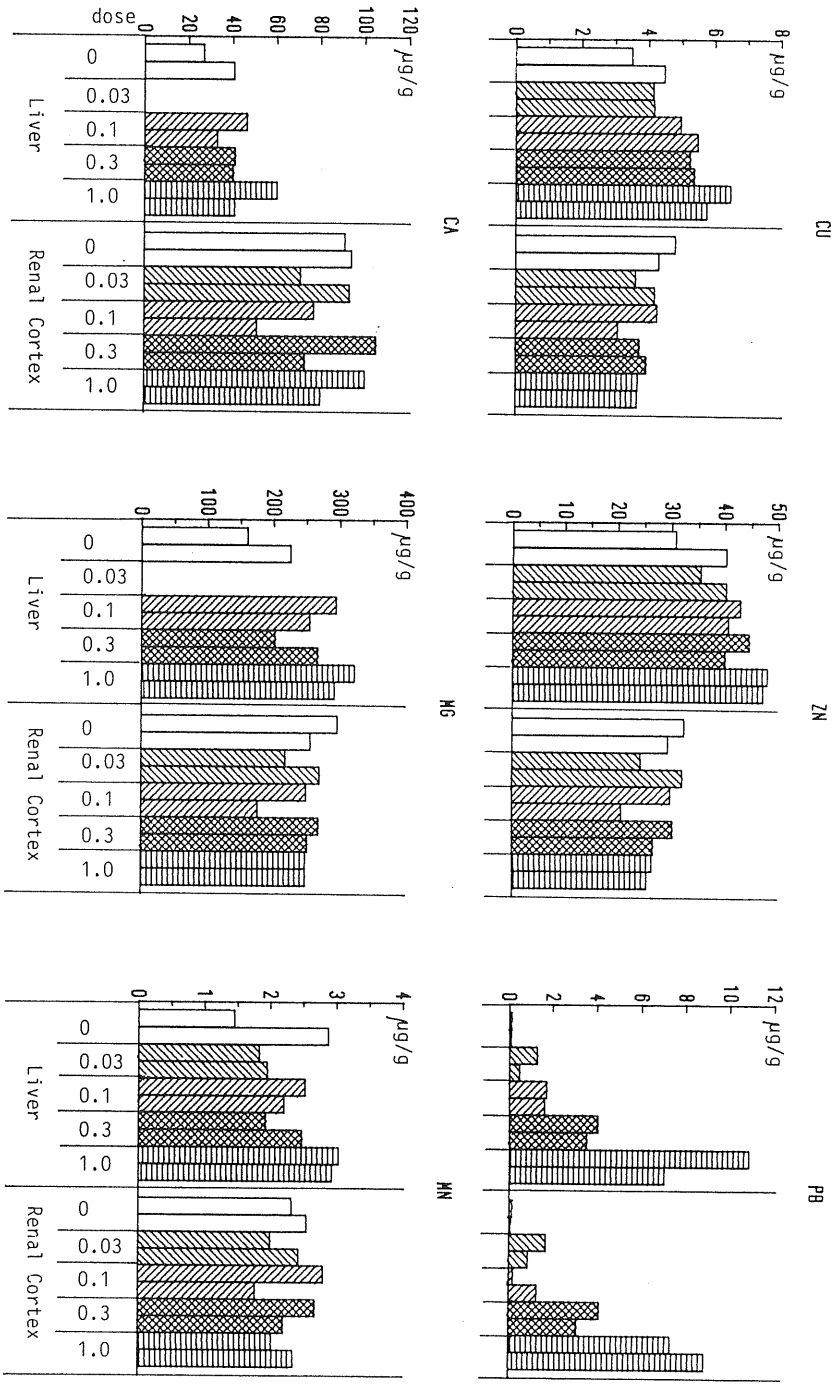

Fig. 2. Dose-effect relationships for tissue trace element shifts by lead in rabbits. Unit of lead dose: mg/kg.

Thirty-three rabbits of another group were given daily subcutaneous injections of cadmium chloride at a dose of 0, 0.1, 0.25 or 0.5mg/kg body weight for 34 weeks. Fifteen trace elements in the liver and the kidneys were analysed by atomic absorption spectrophotometry and induced-coupled plasma emission spectrophotometry. Plasma zinc and copper elevated right after cadmium treatment regardless of the dose, but decreased a little earlier than the appearance of cadmium health effects. The decrease was observed earlier in a higher dose level. As shown in Fig. 3, tissue copper and zinc levels were also elevated soon after cadmium treatment, but decreased a little later than the decrease in plasma copper and zinc. Tissue lead, cobalt and nickel were also elevated in a dose-effect relationships, and decreased after the appearance of health effects. On the contrary, tissue aluminum decreased, and then increased. Other tissue trace elements, such as magnesium, iron and molybdenum, were decreased. Most tissue trace elements shifted in a dose-effect relationship.

Nine male crab-eating monkeys were fed with normal diet, cadmium-polluted rice (1.33 μg/g)or pelleted food containing cadmium chloride at a level of 3 μg/g over a period of 6 years. Sixteen trace elements in the liver and the kidneys were analysed by atomic absorption spectrophotomerty and induced-coupled plasma emission spectrophotometry. No cadmium health effects were observed in either group. Tissue copper and zinc were elevated with the dose of cadmium, but not depressed yet. It is, therefore, difficult to forecast the cadmium health effects in the future.

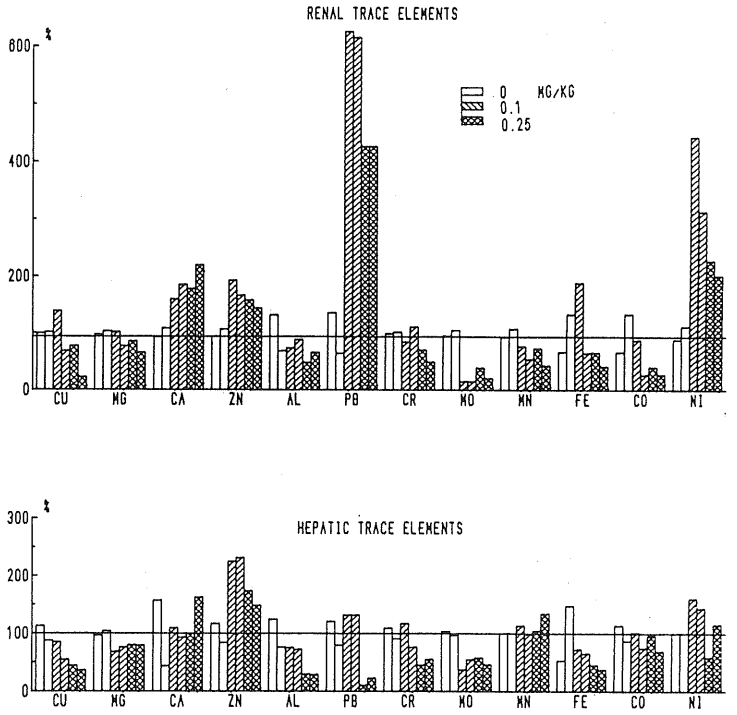

Fig. 3. Dose-effect relationships for tissue trace element shifts by cadmium in rabbits.

2. Aggravated health effects of heavy metals by copper or zinc deficiency[6,7]

1) Cadmium (Fig. 4)

The above results suggest that zinc or copper deficiency might aggravate the effects of cadmium.

Rats, fed with copper deficient diet, could not survive over 6 weeks in the preliminary experiment[6], and this diet was used in the following experiment.

Thirty-eight male rats of Fischer strain, 4 weeks old, were divided into 3 groups, which were fed with normal, copper insufficient or zinc deficient diet for 3 weeks. Diet intake was 15 g/day. Then, they were given subcutaneous injections of cadmium chloride at a dose of 0, 0.3 or 1.0 mg/kg body weight 6 times a week for another 3 weeks. Zinc deficiency aggraveated health effects of cadmium in rats: increased liver, kidney and spleen weight, remarkably elevated plasma alkaline phosphatase, elevated lactate dehydrogenase and cholesterol and slightly elevated urinary amino acids as well as slightly depressed plasma protein. On the contrary, health effects of cadmium were not aggravated in copper insufficiency.

2) Mercury

Thirty-eight male rats of another group were devided into 3 groups, which were fed with the same three types of diets for same duration as above. Then, they were given subcutaneous mercury chloride injection at a dose of 0, 0.5 or 2.0 mg/kg body weight 6 times a week for another 3 weeks. Zinc deficiency aggravated health effects of mercury, specifically body weight, renal functions and protein metabolism, in rats: remarkable loss of body weight followed by higher accumulated rate of death in the 2 mg/kg group, and remarkably increased kidney weight and remarkably decreased thymus weight and plasma urea nitrogen, and elevated urinary amino acids, increased liver weight, and slightly depressed plasma protein and alkaline phosphatase. Copper insufficiency did not aggravate mercury health effects.

The above data may indicate how dietary intake of zinc and copper play an important role in helath effects of heavy metals, environmental pollutants.

3. Alleviated health effects of heavy metals by copper supplementation[8]

On the contrary to the above results, excess intake of copper may alleviate health effects of heavy metals.

Thirty-three rabbits were divided into 3 groups: the first group were given subcutaneous administrations of cadmium chloride at a dose of 0.5 mg/kg body weight daily for 24 weeks, the second group were treated similarly in addition simultaneous intravenous administration of copper sulfate at a dose of 50 μg/kg body weight once a week for 24 weeks, and the last group served as contorl. Copper supplementation alleviated health effects of cadmium, such as body weight loss, renal dysfuntions as well as tissue trace element shift as seen in Fig. 5. In the copper supplemented group, almost no body weight loss was observed. The increase in urinary protein, glucose and amino acids delayed 1–4 weeks compared with the cadmium group. The increase in plasma aspartate

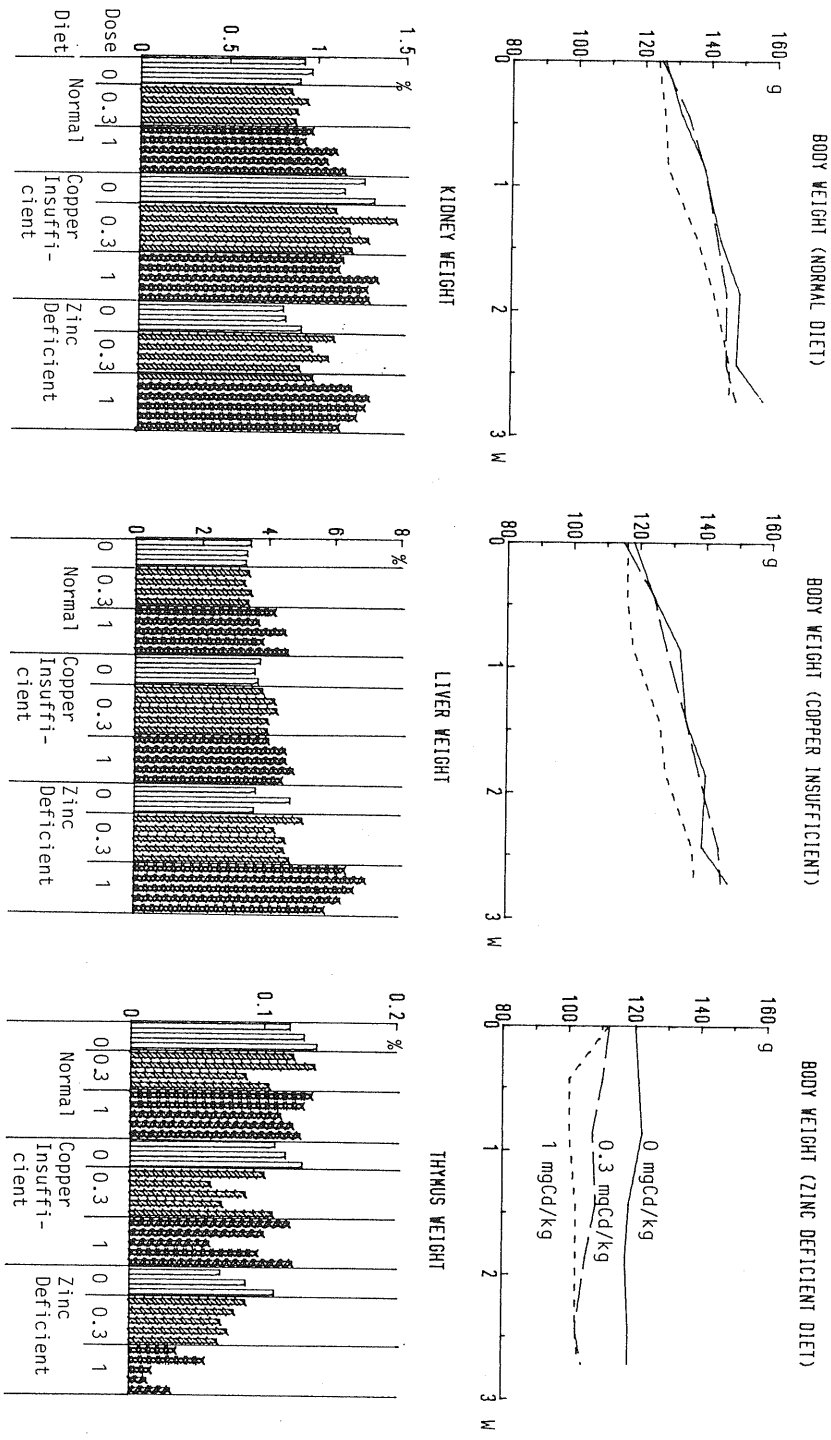

Fig. 4. Aggravated health effects of cadmium in zinc deficient and copper insufficient rats. Unit of cadmium dose level: mgCd/kg. Organ weights represent a ratio of organ weight to body weight.

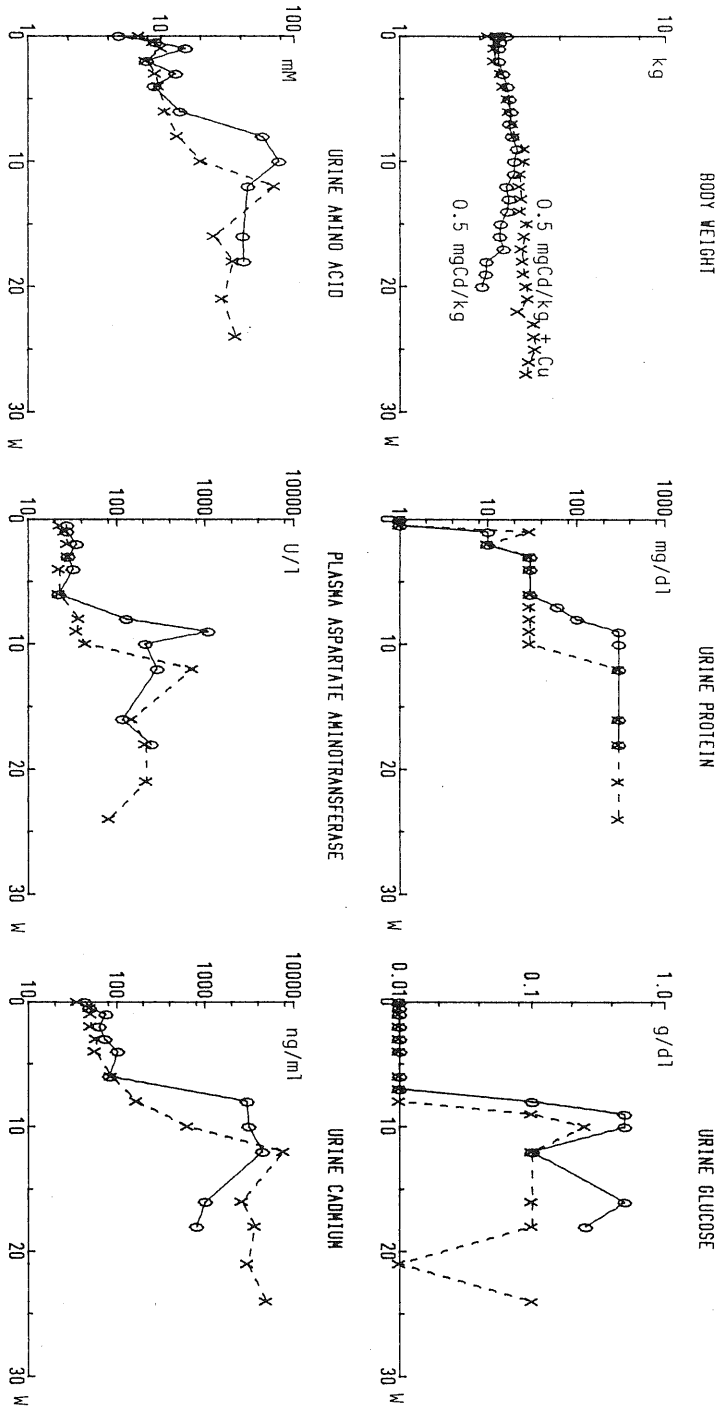

Fig. 5. Alleviated health effects of cadmium by intravenous copper supplementation in rabbits.

aminotransferase, alanine aminotransferase and γ-glutamyltransferase delayed by 3 weeks. Urinary cadmium, copper and zinc increased later than the cadmium group as well.

The above data may indicate how important to improve our daily intake of copper by diet is, to survive in chemically-contaminated environment.

4. Tissue trace element shifts by chronic exposure to organic solvents[9]

Fifty-two male rats of Sprague-Dawley strain, 6 weeks old, were exposed to 0, 50, 200 or 800 ppm trichloroethylene for 12 weeks, and then their tissue trace elements were determined. Other rats were also exposed to same levels of tetrachloroethylene or 1,1,1-trichloroethane, or 0, 200, 800 or 3,200 ppm Flon 113 (1,1,2-trichloro-1,2,2-trifluoroethane).

Trichloroethylene elevated tissue copper, zinc and magnesium, while tetrachloroethylene elevated tissue copper, magnesium and iron. 1,1,1-Trichloroethane depressned only renal calcium. Flon 113 depressed tissue zinc, copper, magnesium, calcium and mangaese.

The mechanism of tissue trace element shifts by chronic exposure to organic solvents, remains unclear so far.

5. Stress-induced tissue trace element shifts[10]

Stress also induced tissue trace element shifts. Dexamethazone was used as a stress agent in the present experiment.

Six rats of Sprague-Dawley strain, 4 weeks old, were divided into 2 groups: the first group were given a single intraperitoneal injection of dexamethazone at a dose of 4 mg/kg body weight, and the other group received saline. Twenty-four hours after the injection, the health effects and tissue trace elements of the animals were investigated.

Dexamethazone elevated hepatic zinc, as was discussed by Cousins *et al.*[11]

6. Aging aggravates cadmium health effects, in association with trace element insufficiency[12]

It has been known that elderly people are somewhat in trace element insufficient state, which cause hyposmia, taste blindness or osteomalacia. The present study was performed to clarify how aging aggravate cadmium health effects, in assoication with trace element insufficiency.

Sixty-three male rabbits of Japanese white strain, 1, 17 or 73 weeks old, were given subcutaneous injections of cadmium chloride at a dose of 0, 0.1 or 0.25 mg/kg body weight 5 times a week for 24 weeks. Cadmium health effects were more remarkable in older rabbits (Fig. 6). Blood and plasma copper and zinc levels were elevated with cadmium administration, and then decreased a little before cadmium health effects became apparent. Urine cadmium, copper and zinc were elevated earlier in older rabbits. Hepatic and renal cadmium was elevated with the dose of cadmium, and then decreased in the order of age, earlier in older rabbits. Another mechanism of age-related aggravation of cadmium toxicity is the depressed metallothionein induction. Less metallothionein in the tissues of older rabbits could not detoxicate all the tissue cadmium, and, therefore, excessive

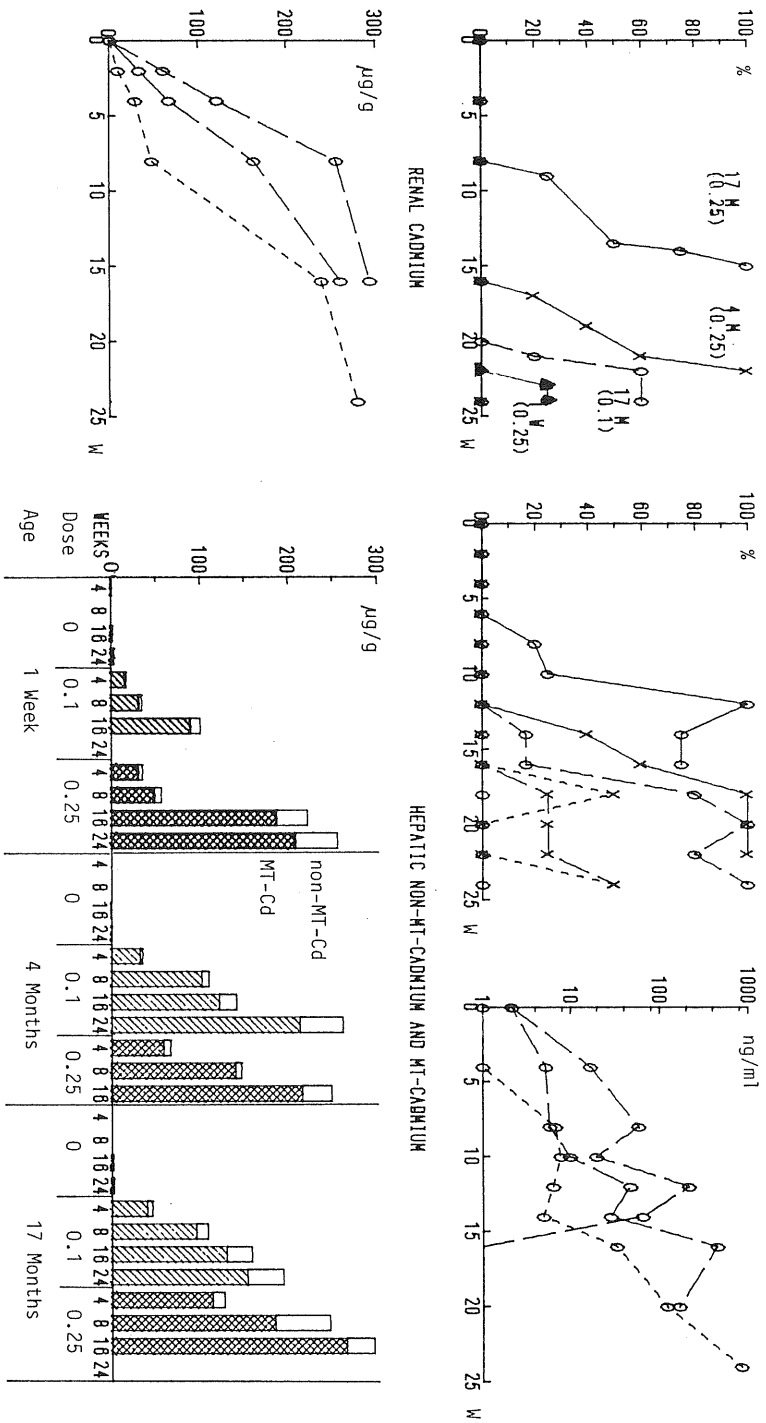

Fig. 6. Aggravated health effects of cadmium by aging, and its mechanism.

"active" cadmium, probably ionic cadmium[13], may aggravate cadmium health effets in older rabbits.

7. Tissue trace element shift by a single exposure to metals[10,14]

Precious metals have been used as anti-carcinogenic and anti-rheumatic agents, even though the precise mechanism is not clear. This situation urged us to study tissue trace element shifts by metals.

Eighty-two rats of Sprague-Dawley strain, aged 7 weeks, were given a single intravenous injection of copper, silver, gold, zinc, cadmium, mercury, lead, arsenic, selenium, platinum as well as 2 organic gold and an organic platinum, at a one-fifth median lethal dose. Twenty-four hours after the injection, their health effects as well as 13 hepatic and renal trace elements were studied. Tissue copper was elevated by copper, cadmium, arsenic, gold, and organic gold, and tissue zinc was elevated by zinc, mercury, silver, gold and organic gold as shown in Table 1. Renal molybdenum was remarkably depressed by mercury, lead or silver probably due to renal dysfunctions. Renal cobalt was also elevated by copper, silver, selenium and arsenic.

Table 1. Tissue trace element shifts by a single exposure to heavy metals

Element	Tissue	Treatment
Cu	Liver	Cu, (Ag, Zn)
	Kidney	Cu, Au, As, Auranofin
Ca	Liver	Ag, Au, Au thiomalate
	Kidneys	Au, Pb
Zn	Liver	Ag, Au
Mn	Liver	Most treatment
	Kidneys	Cu, Ag, Au, Zn, Cd, Pb, Auranofin, Au thiomalate (related to renal damage)
Fe	Liver	Cu
	Kidney	Cu
Co	Liver	Cu, Ag, Se
	Kidney	As, Cisplatin, Au thiomalate

As seen above, shift were observed not only in tissue essential trace elements, such as copper, calcium, zinc, manganese, iron and cobalt, but also in so-called toxic trace elements, such as cadmium and lead, by a single administration of heavy and precious metals in rats.

The above results may indicate the mechanism of gold therapy in rheumatism as follows: gold induces copper shift from the liver to the other organs. The elevated tissue copper inhibits prostaglandin E_2 production and enhances prostaglandin F_2 production. This may reduce pain of rheumatism. Gold therapy may be an indicrect therapy for rheumatism and a less harmless therapy, by comparison with copper therapy.

8. Mechanism of effects of "rasa" mineral drugs in ayurveda medicine, from the viewpoint of tissue metal shift (preliminary result)

"Rasa", mercury drugs, have been used for elderly people to enhance vivacity and to enhance the recovery from chronic diseases in India and Arabian countries. It is apparent that trace amout of mercury does not induce any health effects, because renal mercury dose not reach the critical concentration (50–250 μg/g) due to its short biological half time (70 days). We have a hypothesis that the effects of "rasa" may be associated with enhanced immunity through elevated tissue zinc.

Twinty-three male rats of Sprague-Dawley strain, 7 weeks old, were divided into 4 groups, which were orally given mercury sulfide (II) (black) 15 mg/kg body weight, or black precipitate 15 mg/kg or calomel 1 mg/kg 6 times a week for 12 weeks. Last group were served as control. Health effects and 13 hepatic and renal trace elements were determined. No specific tissue trace element shift were sobserved. The discrepancy between our hypothesis and the experimental results may be explained as follows: 1) the mechanism may be independent of tissue element shift, 2) the period of "rasa" administration was too short, or 3) model mercury drugs, employed in the present experiment, were not suitable, and real "rasa" should be used in future experiments.

CONCLUSION

Acute and chronic exposure to heavy metals, organic solvent and stresses induce tissue trace element shift. Supplementation of copper, and probably zinc in some cases, alleviated health effects of occupational and environmental pollutants. Aging aggravated health effects, on the contrary, probably because of decreased tissue trace elements and depressed vivacity in protein synthesis and others.

These data may indicate that improved diet by taking more trace elements promise healthy life, especially for elderly people.

ACKNOWLEDGEMENTS

This work was supported mainly by Grant-in-Aid Scieintific Research A58440040 from Japanese Ministry of Education, Science and Culture.

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