# What are Trace Elements?
## —Their deficiency and excess states—

JMAJ 47(8): 351–358, 2004

Osamu WADA

*Professor Emeritus, University of Tokyo*

**Abstract:** Elements which are detected in small but not precisely known amounts in the living body were called "trace elements" in the past. Recent advances in analytical technologies, such as the development of atomic absorption spectrometry, have made it possible to measure these elements precisely and to determine their functions and the characteristics of their deficiency and excess states. The so-called vitamin boom has passed, and it now appears to be boom-time for trace elements. Nowadays, cases with trace element deficiencies are often encountered clinically, especially during high-calorie parenteral therapy or enteral nutrition, and congenital abnormalities of trace element metabolism have been clarified successively. Thus, knowledge of the clinical aspects of trace elements is becoming indispensable for front-line clinicians.[1)] Meanwhile, epidemiological surveys and animal studies have suggested the possibility that some trace element deficiencies are associated with a reduced anti-oxidant potential in organisms (which is believed to possibly underlie the onset of cancer and atherosclerosis), accelerated aging, developmental retardation in children, and an increased incidence of abnormal pregnancies, immunological abnormalities, and lifestyle-related diseases. Thus, from the viewpoint of prophylactic medicine, study, survey, and prophylaxis of trace elements are also attracting close attention.

**Key words:** Trace element; Trace element deficiency; Excess of trace elements; Congenital abnormality in trace element metabolism

## What are Trace Elements?

The human body is composed of elements which can be roughly divided into abundant elements and trace elements. Abundant elements consist of the major elements that are involved in the formation of covalent bonds and are important constituents of tissues (oxygen, carbon, hydrogen, nitrogen, etc.), and semi-major elements, which often exist in the ionic state, and are involved in functions of the living body through maintenance of osmotic pressure and membrane potentials (potassium, sodium, etc.). Major elements account for 96%

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 129, No. 5, 2003, pages 607–612).

Table 1 Functions of Trace Elements and Symptoms of Their Deficiency and Excess States

| Trace element | Enzymes containing the elements and active forms | Physiological functions | Symptoms of deficiency state | Symptoms of excess state |
|---|---|---|---|---|
| Zinc | Carbonic anhydrase<br>Peptidase<br>Alcohol dehydrogenase<br>Alkaline phosphatase<br>Polymerase<br>Zinc finger<br>etc. | Protein metabolism<br>Lipid metabolism<br>Carbohydrate metabolism<br>Bone metabolism | Major symptoms:<br>Gradually exacerbating eruptions, first affecting the face and perineum<br>Associated symptoms:<br>Stomatitis, glossitis, alopecia, nail changes, abdominal symptoms (diarrhea, vomiting), fever<br>Delayed wound healing, dwarfism<br>Growth retardation, negative N balance,<br>Immunosuppression,<br>Mental symptoms (depression),<br>Taste disorder, anorexia | Acute:<br>Relative Fe-Cu deficiency, nausea, vomiting, abdominal pain, melena, hyperamylasemia, somnolence, hypotension, lung edema, diarrhea, jaundice, oliguria<br>Chronic:<br>Reduced reproductive function, dwarfism, taste disorder, hyposmia, anemia |
| Copper | Ceruloplasmin<br>Monoamine oxidase<br>Cytochrome oxidase<br>Ascorbic acid oxidase<br>Dopamine $\beta$-hydroxylase<br>Superoxide dismutase<br>etc. | Hemopoiesis<br>Bone metabolism<br>Connective tissue metabolism | Anemia<br>Leukopenia<br>Neutropenia<br>Disturbed maturation of myeloleukocytes<br>Bone changes (children):<br>Reduced osseous age, irregular/spurring metaphysis, bone radiolucency, bone cortex thinning | Nausea, vomiting, heartburn, diarrhea, jaundice, hemoglobinuria, hematuria, oliguria, anuria, hypotension, coma, melena |
| Chromium | Glucose tolerance factor | Carbohydrate metabolism<br>Cholesterol metabolism<br>Connective tissue metabolism<br>Protein metabolism | Abnormal glucose tolerance<br>Reduced respiratory quotient<br>Weight loss<br>Peripheral neuropathy<br>Increased serum free fatty acids<br>Abnormal nitrogen balance<br>Metabolic consciousness disturbance | Nausea, vomiting, peptic ulcer, CNS disorder,<br>Liver/kidney dysfunction, growth retardation |
| Selenium | Glutathione peroxidase (GSH-Px)<br>5′-deiodinase (type I)<br>Various selenoproteins | Antioxidant action<br>T4→T3 conversion<br>Reduced carcinogenicity action | Myalgia (lower extremities)<br>Cardiomyopathy (myocardial cell collapse, fibrosis)<br>Nail bed whitening | Selenosis (alopecia, nail detachment, CNS disorder) |
| Manganese | Arginase<br>Pyruvate carboxylase<br>Superoxide dismutase<br>Glycosyltransferase | Bone metabolism<br>Carbohydrate metabolism<br>Lipid metabolism<br>Reproduction<br>Immunity | Reduced serum cholesterol<br>Reduced coagulation<br>Hair reddening<br>Dermatitis (miliaria crystallina)<br>Growth retardation<br>Increased radiolucency at the epiphyses of long bones | Parkinsonian syndrome<br>Early chronic:<br>Impotence, loss of vigor, somnolence, anorexia, edema, myalgia, headache, excitation, fatigue<br>Advanced stage:<br>Extrapyramidal disorder |
| Molybdenum | Xanthine oxidase<br>Xanthine dehydrogenase<br>Aldehyde oxidase<br>Nitrous acid oxidase | Amino acid metabolism<br>Uric acid metabolism<br>Sulfuric acid/sulfurous acid metabolism | Tachycardia<br>Polypnea<br>Night blindness<br>Scotoma<br>Irritability<br>Somnolence<br>Disorientation<br>Coma | Hyperuricemia, gout |
| Cobalt | Vitamin $B_{12}$ | Hemopoiesis | Pernicious anemia<br>Methylmalonic acidemia | Cobalt poisoning |
| Iodine | Thyroid hormone | Tissue metabolism | Goiter, hypothyroidism | Goiter, hypothyroidism |

(Summary of many reports)

of the total body weight, and the semi-major elements account for 3 to 4% of the total body weight. Deficiency of major elements can lead to nutritional disorders, and their presence in excess can cause obesity. Deficiencies or excess states of semi-major elements often result in water and electrolyte abnormalities.

Essential trace elements of the human body include zinc (Zn), copper (Cu), selenium (Se), chromium (Cr), cobalt (Co), iodine (I), manganese (Mn), and molybdenum (Mo). Although these elements account for only 0.02% of the total body weight, they play significant roles, e.g., as active centers of enzymes or as trace bioactive substances. A major outcome of trace element deficiencies is reduced activity of the concerned enzymes. However, since each trace element is related to so many enzymes, deficiency of a single trace element is often not associated with any specific clinical manifestations, but rather manifests as a combination of various symptoms. Because of the presence of trace elements in very small amounts and the absence of specific clinical features associated with their deficiency, it is often difficult for clinicians to identify deficiencies of some particular trace elements.

Table 1 lists the enzymes containing trace elements, and summarizes the physiological functions of trace elements and the characteristics of their deficiency and excess states.

## Trace Elements as Nutrients or Medicines[2)]

Like vitamins, trace elements were also originally viewed as nutrients. They are listed in the Japanese recommended dietary allowance (RDA). Because of the tendency in recent times towards unbalanced food intake, excessive purification of crops, and dieting practiced widely to reduce body weight, deficiency of zinc (a trace element abundantly contained in animal foods and crops) are encountered relatively frequently.

Trace elements exert pharmacological actions if they are ingested in amounts several to ten times higher than the nutritional requirements. Excessive ingestion of trace elements as medicines has also been reported, which may occasionally lead to poisoning. To avoid such poisoning, the RDA table displays also the reference dose (RfD, i.e., the highest permissible dose) for each element. However, the RfD shown in the RDA table is relevant as reference values only when trace elements are ingested as ordinary nutrients. Table 2[1)] lists the pharmacologically effective actions of trace elements when they are consumed in excess. However, when dealing with trace elements, caution must be exercised to avoid excessive dosage.

Table 2 Trace Elements and the Potential Effects of Replenishment, Prophylaxis, and Pharmacological Effects

| Trace element | Potential effects of replenishment, prophylaxis, and pharmacological effects |
|---|---|
| Iron | Correction of latent iron deficiency<br>Resistance to infections |
| Zinc | Wound healing<br>Improved resistance to infections and immune functions<br>Correction of developmental retardation and gonadal hypoplasia<br>Correction of taste disorder |
| Chromium | Correction of carbohydrate metabolism<br>Prevention of atherosclerosis |
| Selenium | Anti-cancer activity<br>Prevention of ischemic heart disease<br>Vitamin E-like activity |
| Fluorine | Prevention of dental caries |
| Iodine | Correction of latent iodine deficient goiter |

(Quoted from Wada, O. *et al.*: Trace elements and their abnormalities. *Integrated Handbook of Internal Medicine* 6, Nakayama-Shoten Co., Ltd., Tokyo, 1995; pp. 253–263.)

## Daily Intake, Recommended Dietary Allowance, Reference Dose, and Safety Margin of Trace Elements, and Causes of Deficiency States

Table 3[2)] summarizes these parameters in

Table 3 Daily Dietary Requirements of Trace Elements in Adult Japanese Males (body weight: 50 kg)

| Trace element | Mean daily intake | "No adverse effects" level (NOAEL) | "Lowest adverse effect" level (LOAEL) | Effective replenishment/ pharmacological dose | Recommended dietary allowance (RDA) | Reference dose (RfD) | RfD/ RDA |
|---|---|---|---|---|---|---|---|
| Zinc | 7~11 mg | 30 mg* | 600 mg | ~200 mg (immune functions, etc.) | 9.6 mg | 30 mg | 3 |
| Copper | 1~4 mg | 9 mg* | 10 mg | — | 1.8 mg | 9 mg | 5 |
| Chromium (III) | 28~62 μg | 1,000 μg* | — | 150~1,000 μg (diabetes mellitus, etc.) | 35 μg | 250 μg | 7 |
| Selenium | 41~168 μg | 400 μg | 750 μg* | ~200 μg (cancer prevention, etc.) | 55 μg | 250 μg | 4.5 |
| Manganese | 3~4 mg | 10 mg* | — | — | 4 mg | 10 mg | 2.5 |
| Molybdenum | 135~215 μg | 350 μg | 7 mg* | — | 30 μg | 250 μg | 8 |
| Iodine | 200~30,000 μg | 3,000 μg* | 23,000 μg | — | 150 μg | 3,000 μg | 20 |
| Arsenic | 10~34 μg | 40 μg* | 700 μg | — | 10–34 μg | 140 μg | 4 |

*Basis for calculation of RfD
• The mean daily intake is approximately equal to the RDA.
• RfD/RDA indicates the safety margin between daily requirements and toxic levels, and is not very large.
(Quoted from Wada, O.: Usefulness and safety of trace chemicals. *Proceedings of Trace Nutrients Research* 2001; 18: 1–10.)

Table 4 Major Causes of Trace Element Deficiency

1. Inadequate supply
 1) Congenital metabolic disorders: Acrodermatitis enteropathica (zinc), Menkes disease (copper)
 2) Inadequate intake: Unbalanced nutrition, excessive purification of crops, ingestion of foods poor in trace elements, undevelopment of the food transportation system
2. Iatrogenic: High-calorie parenteral therapy, chelating drugs, surgery, etc.
3. Diseases, etc.: Pregnancy, excessive alcohol consumption, liver disease, nephropathy

Note: Underlined factors are predominant.

relation to trace elements. It is noteworthy that the mean daily intake and the RDA are approximately the same for most trace elements. This can be interpreted as evidence that over the long history of humankind, dietary styles allowing approximately stable supply of trace elements have become established, and that the amounts of trace elements ingested via food represent the appropriate levels. In other words, trace element deficiencies are unlikely to occur unless the dietary patterns of individuals change dramatically, or the metabolism of trace elements is disturbed. Table 4 shows the major causes of trace element deficiencies. High-calorie parenteral therapy and enteral nutrition can be viewed as representing dramatic alterations of the dietary pattern, while extremely low intake and congenital metabolic abnormalities can be viewed as representing disturbed metabolism of trace elements. In recent years, the prevalence of these metabolic abnormalities has been on the increase, and their pathophysiology has been clarified in depth, highlighting the importance of trace elements in clinical practice.

It is also important to note that the ratio of the RfD to RDA, i.e., the safety margin, is not very large. Amidst the tendency of people to consume health promotion foods based on their distrust of medicines, preparations of trace elements are available commercially, and inappropriate use of these preparations can cause excess states of these trace elements. It is also noteworthy that the doses at which trace elements exert pharmacologically effective actions are much higher than the RfD.

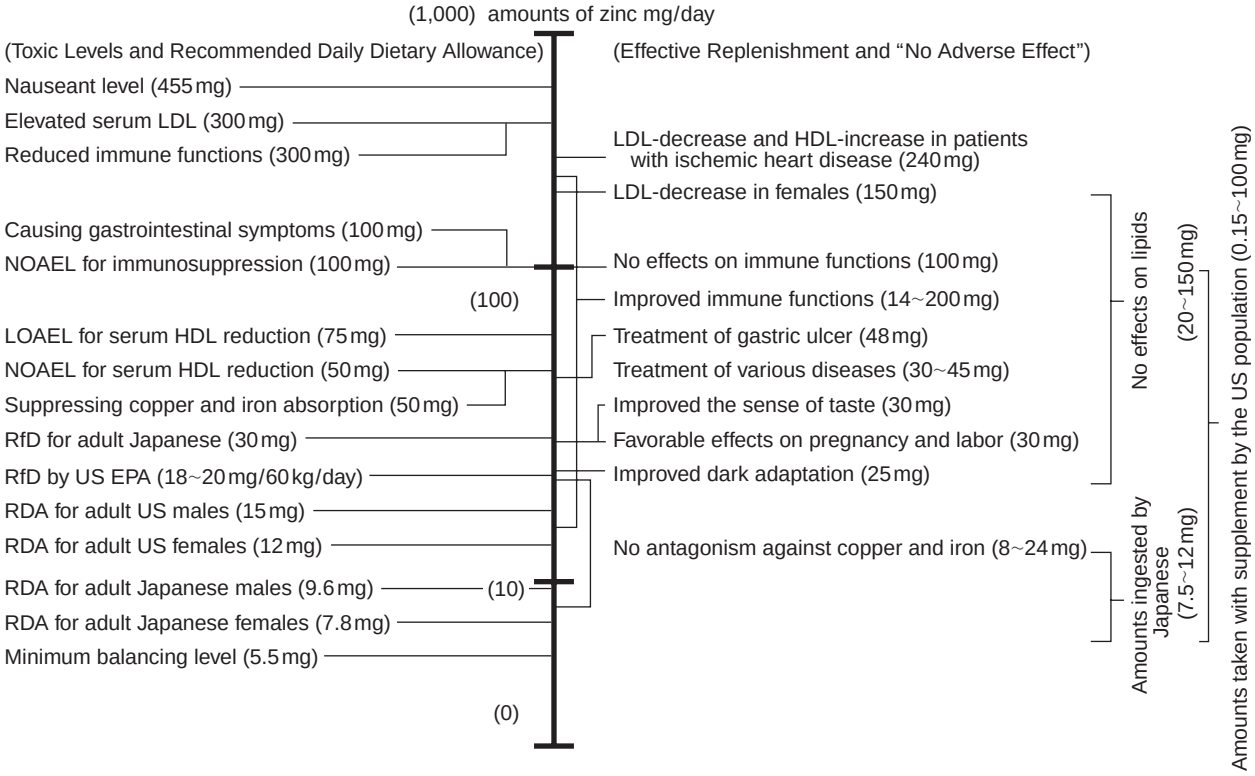



Fig. 1 Toxic levels, recommended daily dietary allowance, effective replenishment dose, and "no adverse effect" level of zinc (amounts of zinc = absolute level)
The effective replenishment level (pharmacological level) is higher than toxic levels. The amount ordinarily ingested is slightly lower than the recommended daily dietary allowance.
(Quoted from Wada, O.: Usefulness and safety of trace chemicals. *Proceedings of Trace Nutrients Research* 2001; 18: 1–10.)

Figure 1 graphically represents these relationships for zinc.[3)]

## Deficiency and Excess States of Trace Elements

As shown in Table 5, deficiency and excess of trace elements are either congenital or acquired. Deficiency states of trace elements are most frequently seen during high-calorie parenteral therapy or enteral nutrition. Zinc deficiency can develop within 2 weeks after the start of such therapies.[4)] Therefore, while administering these therapies, caution must be exercised to ensure that all trace element deficiencies are prevented.

Congenital abnormalities of trace element metabolism are rare. Abnormal intestinal absorption or disturbed transport of absorbed trace elements more often lead to deficiency of trace elements. Acrodermatitis enteropathica due to disturbed zinc absorption and Menkes disease due to abnormal copper transport through the intestinal mucosa[5)] are some examples of such conditions.

If the site of uptake of trace elements into an active form is disturbed, the trace element is pooled there, causing excess of the element. In cases of Wilson disease characterized by disturbed uptake of copper into ceruloplasmin,[5)] tissue damage and fibrosis due to copper occur in the liver and other sites.

## Trace Element Deficiencies as Viewed from the Standpoint of Prophylactic Medicine

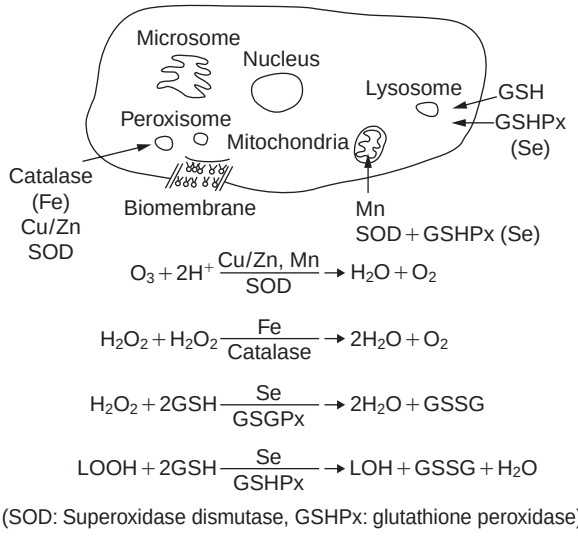
Many epidemiological surveys and animal

Table 5 Clinical Deficiency and Excess States of Trace Elements

| Trace element | Deficiency | | Excess | |
|---|---|---|---|---|
| | Congenital | Acquired | Congenital | Acquired |
| Iron | Atransferrinemia | Iron-deficiency anemia | Hemochromatosis | Iron poisoning |
| Zinc | Acrodermatitis enteropathica | High-calorie parenteral therapy, enteral nutrition, drugs (chelating agents), inadequate intake | | Zinc fume fever, zinc poisoning |
| Copper | Menkes disease Aceruloplasminemia | High-calorie parenteral therapy, enteral nutrition | Wilson disease | Copper fume fever, copper poisoning |
| Manganese | | High-calorie parenteral therapy (1 case) | | Parkinsonian syndrome |
| Selenium | Some types of pancreatic cysts | High-calorie parenteral therapy (several cases), dietary Keshan disease, Kaschin-Beck disease, ischemic heart disease, cancer | | Selenosis |
| Chromium | | High-calorie parenteral therapy (several cases), diabetes mellitus, atherosclerosis | | Chromium poisoning, lung cancer |
| Iodine | Abnormal iodine metabolism | Goiter | | Goiter |
| Cobalt | | Pernicious anemia | | Cobalt poisoning |
| Molybdenum | | High-calorie parenteral therapy (1 case) | | Gout, molybdenum poisoning |

Table 6 Trace Element Deficiency as Viewed from the Standpoint of Preventive Medicine

| What needs to be prevented | Elements involved |
|---|---|
| Reduction in anti-oxidant potential | Zinc, iron, manganese, selenium, copper |
| Promotion of aging and its cause | Zinc, copper, selenium, chromium |
| Developmental retardation of children | Zinc |
| Abnormal pregnancies, infertility, fetal abnormalities | Zinc |
| Immunodeficiency | Zinc, iron, copper, selenium |
| Increased carcinogenicity | Zinc, copper, selenium |
| Promoted atherosclerosis | Zinc, selenium, iron, copper, chromium |
| Increased incidence of diabetes mellitus | Chromium, zinc, selenium, vanadium |
| Predisposition to hypertension | Copper, zinc, selenium |
| Predisposition to senile dementia | Zinc |
| Predisposition to taste disorder | Zinc |
| Predisposition to dental caries | Fluorine |
| Predisposition to goiter | Iodine |




(SOD: Superoxidase dismutase, GSHPx: glutathione peroxidase)

Fig. 2 Anti-oxidative actions of trace elements
The characteristics of trace element deficiency, especially in the case of adults, may be explained by a reduction in the anti-oxidant actions.
(Quoted from Wada, O.: Trace elements and sugar and lipid metabolism — Overview. *Endocrinology & Diabetology* 1998; 6: 109–117.)

Table 7 Diagnosis of Trace Element Deficiency

1. Trace element deficiency is one of the most difficult conditions to diagnose.
   Few valid methods are available (due to the wide overlap between the normal state and the deficiency state).
2. Methods currently used
   1) Measurement of trace element concentrations in samples:
      serum, erythrocytes, leukocytes, lymphocytes, hair (for many elements); urine (for iodine)
   2) Measurement of the activity of enzymes containing trace elements in their core:
      alkaline phosphatase (zinc), 5′-nucleotidase (zinc), ACE ratio (zinc),
      ceruloplasmin (copper), thyroid hormone (iodine), glutathione peroxidase (selenium), etc.
3. Function tests: dark adaptation (zinc), taste test (zinc), electroretinogram (zinc)
4. Balance studies: many elements, not practical
5. Analysis of daily intake: not practical, large variance (many elements)
6. Checking for alleviation of symptoms following replenishment:
   most reliable method of diagnosing deficiency (many elements)

Note: Underlined methods are the most frequently used.
(Quoted from Wada, O. *et al*.: Trace elements and their abnormalities. *Integrated Handbook of Internal Medicine* 6, Nakayama-Shoten Co., Ltd., Tokyo, 1995; pp. 253–263.)

studies have demonstrated that health problems are caused by deficiency of trace elements (Table 6).[6] It has been shown that the deficiency of many trace elements, especially zinc, is associated with accelerated aging,[7] immunodeficiency,[8] accelerated progression of HIV infection,[9] increased incidence of abnormal pregnancies,[10] developmental retardation in children,[11] and taste disorder.[12] It has also been shown that deficiency of chromium[13] is related to the development of diabetes mellitus and atherosclerosis, and that selenium deficiency[14] is associated with the increase of cancer and ischemic heart disease. Clarifying these abnormalities clinically and establishing countermeasures against them are important issues that must be addressed by regional hospitals engaged in both prophylactic medicine and clinical medicine. Studies in this field may be expected to advance rapidly from now on and contribute to improving the dietary habits of populations in local communities.

Decreased anti-oxidant potential of the living body, which is a subject that has recently attracted close attention, is thought to underlie the development of numerous lifestyle disease conditions. Several trace elements have been shown to be involved in the anti-oxidant efficacy of the body (Fig. 2).[13]

## Conclusion

In this article, the basic biology of trace elements and features of their deficiency and excess states have been presented to provide an overview of these elements. Clinically, as well as in nutritional evaluations, one of the most difficult problems concerning trace elements is the difficulty of diagnosing trace element deficiencies. Although the currently available methods of diagnosis are listed in Table 7, there are few methods that allow accurate diagnosis, especially in cases with mild to moderate deficiency. The development of more accurate methods is an issue that must be addressed in future.

### REFERENCES

1) Wada, O. *et al.*: Trace elements and their abnormalities. *Integrated Handbook of Internal Medicine* 6, Nakayama-Shoten Co., Ltd., Tokyo, 1995; pp. 253–263. (in Japanese)
2) Wada, O.: Usefulness and safety of trace chemicals. *Proceedings of Trace Nutrients Research* 2001; 18: 1–10. (in Japanese)
3) Wada, O. and Yanagisawa, H.: Trace elements, with special reference to the usefulness and safety of zinc. *Medicine and Drug Journal* 1997; 33 (12): 126–134. (in Japanese)

4) Takagi, Y. and Okada, T.: Metabolism of trace elements. *Japanese Journal of Clinical Medicine* 2001; 59 (extra issue): 401–412. (in Japanese)
5) Okabe, M. *et al.*: Front-line of research on copper. *Vitamin* 2001; 75: 557–563. (in Japanese)
6) Wada, O. *et al.*: Trace element deficiency in humans. *JJPEN* 1990; 12: 419–424. (in Japanese)
7) Wada, O.: The role of trace elements in aging process. In *Nutrition and Aging*, Intnl Life Sci Institute, Tokyo, 1995; p. 85.
8) Kodama, H.: Role played by essential trace elements in maintenance of immune function. *Japanese Journal of Clinical Medicine* 1996; 54: 46–51. (in Japanese)
9) Patrick, L.: Nutrients and HIV: Part two-vitamins A and E, zinc, B-vitamins, and magnesium. *Altern Med Rev* 2000; 5: 39–51.
10) Shah, D. and Sachdev, H.P.: Effect of gestational zinc deficiency on pregnancy outcomes. *Br J Nutr* 2001; 85 (Suppl 2): S101–S108.
11) Bhandari, N. *et al.*: Effect of micronutrient supplementation on line on growth of children. *Br J Nutr* 2001; 85 (Suppl 2): S131–S137.
12) Tomita, H.: Taste disorder and diet. *Kodansha + αBook*, Kodansha, Ltd., Tokyo, 2002. (in Japanese)
13) Wada, O.: Trace elements and carbohydrate and lipid metabolism — Overview. *Endocrinology & Diabetology* 1998; 6: 109–117. (in Japanese)
14) Schrauzer, G.N.: Anticarcinogenic effects of selenium. *CMLS* 2000; 57: 1864–1873.