10.
Manganese

The following account is based principally upon three recent reviews (1–3).

10.1 Biochemical function

Manganese is both an activator and a constituent of several enzymes. Those activated by manganese are numerous and include hydrolases, kinases, decarboxylases and transferases, but most of these enzymes can also be activated by other metals, especially magnesium. This does not apply, however, to the activation of glycosyltransferases nor possibly to that of xylosyltransferase. Manganese metalloenzymes include arginase, pyruvate carboxylase, glutamine synthetase, and manganese superoxide dismutase.

10.2 Deficiency and toxicity

Manganese deficiency has been produced in many species of animals, but not, so far, in humans. Signs of manganese deficiency include impaired growth, skeletal abnormalities, disturbed or depressed reproductive function, ataxia of the newborn, and defects in lipid and carbohydrate metabolism.

Unequivocal evidence of manganese deficiency in humans has not so far been reported, but a possible case of such deficiency was described by Doisy (4). A man fed a semipurified formula diet found to be low in manganese (0.35 mg/day) lost weight and suffered depressed growth of hair and nails, dermatitis and hypocholesterolaemia, but responded to being fed a mixed hospital diet; supplementation with manganese alone was not tried.

Another possible case of manganese deficiency in humans was reported by Friedman et al. (5). Men fed a diet containing only 0.11 mg of manganese/day for 39 days exhibited decreased serum cholesterol and a fleeting dermatitis (miliaria crystallina). Calcium, phosphorus and alkaline phosphatase activity in blood increased. However, because short-term manganese supplementation (10 days) did not reverse these changes, the suggestion that the syndrome was attributable to manganese deprivation was not substantiated.

Other possible signs of manganese deprivation have been reported (1, 3). A diabetic patient who was not responsive to insulin injections responded to oral
manganese with decreased blood glucose concentrations. In addition, whole­blood manganese concentrations have been reported to be low in patients with certain types of epilepsy.

Manganese is often considered to be among the least toxic of the trace elements when administered orally. Thus, reported cases of human toxicity caused by oral ingestion of large amounts of manganese are few. The most common form of manganese toxicity is the result of chronic inhalation of large amounts of airborne manganese in mines, steel mills and some chemical industries (6). The major signs of manganese toxicity in animals are depressed growth, depressed appetite, impaired iron metabolism and altered brain function (1). Signs of toxicity in Chilean manganese miners were first manifested in the form of severe psychiatric abnormalities, including hyperirritability, violent acts and hallucinations; these changes were called manganic madness (6). As the disease progressed, there was a permanent crippling neurological disorder of the extrapyramidal system with morphological lesions similar to those of Parkinson disease (6).

10.3 Epidemiology of deficiency and toxicity

The natural incidence of effects attributable to abnormal manganese nutrition is apparently exceedingly low. It has been suggested that the high incidence of cartilage disorders in children in some geographical areas may be the result of low intakes of manganese (7).

10.4 Assessment of status

Keen et al. (3, 8) have suggested that the blood manganese concentration may be useful in assessing status because low blood concentrations in manganese­deficient rats reflected low concentrations of manganese in soft tissue. This suggestion is supported by the finding that whole­blood manganese concentrations are elevated with excessive manganese intake in humans (9). Normal whole­blood manganese in humans is apparently about 8.4 μg/l (9).

Urinary manganese may also be an indicator of manganese status. Young men who were fed 0.11 mg of manganese/day for 39 days exhibited a sharp drop in urinary manganese excretion, namely from about 8.6 μg/day to about 0.9 μg/day (5). Upon repletion with 1.53–2.55 mg of manganese/day for 10 days, urinary manganese excretion increased to about 4.0 μg/day. These changes, however, may merely reflect recent diet history.

Further investigation might show that both the activity of manganese superoxide dismutase and the ratio of manganese superoxide dismutase to copper–zinc superoxide dismutase could serve as indicators of manganese
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status, since these two variables, when measured in the livers of rats, were responsive to manipulations of dietary manganese intake (10).

10.5 Absorption and bioavailability

For many species, including humans, it has been assumed that manganese absorption is independent both of body manganese status and of dietary manganese content. This assumption has had to be extensively revised in the light of recent work with rats (11). For example, it was shown that the efficiency of absorption declined from 29% to 2% as dietary manganese increased from 1.5 to 100 μg/g, direct evidence that both true absorption and endogenous faecal excretion vary markedly in homeostatic response to dietary manganese. Thus, the often-cited hypothesis that manganese homeostasis is regulated mainly by a variable excretion via the digestive tract may have to be discarded.

In the rat, intestinal manganese absorption is a rapidly saturable process probably mediated by a high-affinity, low-capacity active transport system (12). In patients with varying iron stores and subjected to duodenal perfusion with manganese, the rate of manganese absorption was found to increase in iron deficiency. The enhanced manganese absorption was inhibited by iron (6). Apparently, the mechanisms involved in the absorption of manganese are very similar to those involved in that of iron.

Dietary fibre is believed to have the greatest negative effect on manganese bioavailability (2), but this hypothesis is in conflict with the results of a balance study in which 12 men consumed two diets containing different amounts of dietary fibre in natural foods for 6 weeks each in a crossover design (13) and the overall manganese balance was found not to be significantly affected by such differences in fibre content.

10.6 Dietary intake

Diets high in unrefined cereals, nuts, leafy vegetables and tea will be high in manganese; diets high in refined grains, meats and dairy products will be low. Such differences are typified by the finding that Indian diets high in foods of plant origin supplied an average of 8.3 mg of manganese/day (14), whereas highly refined hospital diets in the United States supplied a range of less than 0.36–1.78 mg of manganese/day (15). Most other reported mean intakes of manganese throughout the world fall between those values. For example, the mean daily manganese intake of adults consuming self-selected diets was 3.1, 2.7 and 2.9 mg in Canada, New Zealand and the United States, respectively (16–18). A mean intake of 5.1 mg/day has been reported for adults in the United Kingdom (19).
10.7 Requirement and tolerable intakes

Average basal or normative requirements for manganese cannot be established because the data required for this purpose are not available. Attempts to produce manganese deficiency by feeding diets providing as little as 0.74 mg/day (5) or 1.0 mg/day (20) resulted in neither conclusive nor marked effects on the health of adults. The threshold toxicity level is also unknown. Thus, a safe range of mean population intakes for manganese cannot be proposed.

However, Friedman et al. (5) suggested that the minimal requirement for manganese based on obligatory losses in young men consuming a semipurified manganese-deficient formula diet was 0.74 mg/day. Another study done in the same laboratory (21) found negative retention of manganese at dietary intakes of 1.21, 2.06 and 2.89 mg/day, but positive retention at 2.65 and 3.79 mg/day. Based on regression analysis of intake versus balance, an intake of 3.5 mg/day was recommended. This value is difficult to reconcile with the fact that many dietary intakes are close to 2.5–3.0 mg/day, yet no evidence that manganese deficiency is a problem has appeared. Data like these were used to set a safe and adequate intake of 2.0–5.0 mg/day for adults in the United States (22). Whether the lower limit of the safe range of population mean intakes for manganese is in this range remains to be determined.

10.8 Recommendations for future studies

The essentiality of manganese for animals is established beyond question but instances of nutritional deficiency in human subjects have not been unequivocally identified. A legacy of analytical problems has also hindered both the identification of subjects exposed to dietary deficiency of manganese and the circumstances under which a low availability of the element from the diet can be expected. The continuing scrutiny of the experimental evidence of the pathological effects of deficiency is recommended with a view to subsequent epidemiological studies under circumstances that indicate that the dietary intake of available manganese may be low.

References

Manganese cannot be established as available. Attempts to measure as little as 0.74 mg/day for marked effects on the minimal requirement for manganese is 2.65 and 3.79 mg/day. Whether necessary to set a safe and the diet can influence the uptake of manganese was also hindered both dietary and environmental evidence that manganese was not used to set a safe and 20. Johnson PE, Lykken GL. Manganese and calcium balance and absorption in women fed two levels of Ca and Mn. FASEB journal, 1989, 3: A760.
