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The newer essential trace elements, chromium, tin, vanadium, nickel and silicon

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Introduction

Although markedly different in their chemistry, mode of action, and effective levels, the newer essential trace elements have in common that they were first known for their toxic actions in excessive concentrations and that the induction of a dietary deficiency is very difficult. (Although not a trace element in the strict sense, silicon is included in the discussion because of its low concentration in the animal organism.) Deficiencies severe enough to cause death have not yet been demonstrated for any of these, and this fact has necessitated the adoption of a new, more liberal definition of essentiality.

Chromium was identified as essential for maintenance of normal glucose metabolism in 1959. It is not surprising, therefore, that more biochemical and nutritional information is available for this element than for the others. The rapid sequence of discoveries identifying essential functions for new elements which began in 1970 was based on the concepts of the low-trace-metal environment and of the metal-free isolator system for raising animals (Schwarz, 1970). Through the application of these systems and with advances in trace element analytical techniques, the essentiality of four elements, tin, vanadium, nickel, and Si, was demonstrated within a period of only 3 years.

Essentiality

Several definitions of essentiality for trace elements have been proposed (Hoekstra, 1972). Most of these agree on the following criteria: (1) the essential element must be present in living matter; (2) it must be able to interact with living systems; (3) a dietary deficiency must consistently result in a reduction of a biological function from optimal to suboptimal, preventable or reversible by physiological amounts of this element (Mertz, 1972). This latter criterion places heavy emphasis on the distinction between the scientific term 'essentiality' and the practical term 'importance' for animal or human health. The severity of a deficiency sign is of little importance in establishing the essentiality of an element; it is no more than an expression of the degree of deficiency that can be induced with the means currently available. The practical importance of an element, on the other hand, is judged by the relation of the individual requirement to the occurrence of the element in food, water and air; this ratio may vary from one location to another and depends, in addition, on complex nutrient interactions.

The demonstration that the criteria for essentiality are met in several different animal species can serve as a basis for careful extrapolation that the element may be essential for others, including man. This extrapolation does not in any way suggest that actual nutritional problems exist under ordinary conditions. It would be wrong, however, to assume that, because of the difficulty of inducing deficiencies of the newer trace elements, such practical problems do not exist. The existing knowledge of the symptomatology of trace element deficiencies, of optimal requirements and of the influence of nutrient interactions on requirements, is clearly inadequate to rule out the occurrence of practical nutritional problems.

Do the new trace elements meet the criteria of essentiality?

All elements discussed here can be detected in the biosphere if modern, sensitive methods of analysis are used. Reports of non-detectable levels of some of these in certain tissues (for example, of Sn in the newborn) have to be interpreted with great caution, in view of the known analytical difficulties. Organic complexes of Sn and Cr are quite volatile and do not withstand dry ashing. Similar difficulties may exist for the remaining newer trace elements, particularly when measurements in the range of ng/g are involved. For this reason, the values in Table 1 should be considered only as rough approximations subject to correction when our existing analytical capability can be improved.

Table 1. *Estimated concentrations of the newer trace elements in human blood and urine, the daily intake of man, and the estimated requirement of animals*

	Chromium	Tin	Vanadium	Nickel	Silicon
Blood (μg/l)	0·5–5	140	10	3–8	1000–5000
Urine (μg/l)	5–10	10–20	nd–10	10–100	15 000
Daily intake of man (μg)	5–100	1000–4000	—	300–900	10 000–50 000
Estimated requirement of animal species (mg/kg diet)	>0·1	~1·0	>0·1	0·03–3·0	5·0–100

nd, not detectable.

Some form of interaction with living systems has been demonstrated for each of the newer trace elements discussed here. Si is present in certain mucopolysaccharides as part of the very stable bond $-R_1\text{-O-Si-O-}R_2-$ or $-R_1\text{-O-Si-O-Si-O-}R_2-$, and as such may play an important role in the structural configuration of these macromolecules. Cr, Sn, V and Ni have strong tendencies for co-ordination which render them reactive with almost any biological material. All are known to exist in more than one valence state. Although it is unlikely that Cr and Ni occur in living matter in other than their most stable states (+3 and +2, respectively), oxidation–reduction reactions are theoretically possible for Sn (between +2 and +4) and for V (among +3, +4, and +5), thus potentially enabling these metals to participate in biological charge-transfer reactions. Many co-ordination geometries are known for these elements, but it may be speculated that the predominant forms in biological materials may be the octahedral one with a co-ordination number of 6 for Cr and V and a

tetrahedral or coplanar one with a co-ordination number of 4 for Sn. Ni, on the other hand, is known to occur in many different, often unusual configurations, the equilibrium of which is dependent on many outside influences. Furthermore, Cr is characterized by its very slow rate of ligand exchange, and its pronounced tendency to form olated, polynucleate compounds. Another factor important for the mode of participation of these elements in biochemical reactions is the transition from high-spin to low-spin states, which adds another aspect of specificity in the biological action of each of the elements. These considerations suggest that, on the basis of co-ordination chemistry alone, each of the elements could function in a highly specific way in biological systems (Cotton & Wilkinson, 1966).

In addition, each of the newer trace elements has its own pattern of interaction with living matter in vitro. Most inhibit enzyme systems in vitro when given in excessive concentrations. In addition, Cr, V and Ni can activate certain enzymes in vitro, although this effect is most probably non-specific. The high concentrations of Cr and Ni and their firm binding in nucleic acids, and the demonstration of their protective effect against heat-induced conformational changes, suggest that these elements may possibly play an important role in vivo as well. The exceptionally high concentration of Si in some glycosaminoglycans, for example, in hyaluronic acid (1892 μg/g), chondroitin sulphates, and some polyuronides (pectin from citrus fruit, 2586 μg/g) but not in polyglycans such as glycogen, starch and dextran, suggests a biological function, as much of the Si in hyaluronic acid and pectin is so firmly bound that it can be removed only by very rigorous alkaline hydrolysis.

Although these findings are suggestive of a specific role for these elements, the proof of essentiality can be derived only from the demonstration of a deficiency. Experimental deficiencies have been induced in animal species for all five of the newer trace elements. While this was possible for Cr by feeding low-Cr diets to rats in a conventional environment, deficiencies of the remaining four elements have been induced mainly in a controlled environment (metal-free isolator or laminar flow system).

Cr. For reviews, see Hambidge (1974), Mertz (1974*a*). This element was identified as the active ingredient of a dietary agent, glucose tolerance factor (GTF), which is required for maintenance of normal glucose metabolism in the rat. The first detectable sign of Cr deficiency in rats and squirrel monkeys is an impairment of intravenous glucose tolerance, preventable by dietary supplementation with Cr, and reversible by oral administration of a variety of Cr compounds. More severe Cr deficiency results in slightly decreased growth rates and life span, in increased concentrations of serum cholesterol, increased formation of aortic plaques and, under certain conditions, in a syndrome resembling diabetes mellitus, with fasting hyperglycemia and glycosuria. The primary biochemical lesion in Cr deficiency that may be responsible for most, if not all, of the signs observed is the decreased sensitivity of peripheral tissue to exogenous or endogenous insulin. In the absence of insulin, Cr-deficient animals or isolated tissues do not differ significantly from normal controls in any of the indices measured. On the other hand, the response to varied doses of insulin in vitro and in vivo is significantly inferior in Cr-deficient systems,

and much higher doses of the hormone are required to elicit metabolic responses similar to those observed in Cr-sufficient controls. In vitro addition of effective Cr compounds, such as GTF, to epididymal fat tissue of Cr-deficient rats can increase the slope of tissue response to insulin (measured by CO_2 production from glucose) by a factor of 5–10. These findings indicate that Cr is not an insulin-like agent, but a true potentiator of the action of the hormone.

Marginal Cr deficiency, as evidenced by Cr-responsive impairment of glucose tolerance, does exist in man, but its extent cannot be defined exactly at the present time. The few available results of studies in adults suggest that less than half of the subjects studied responded to supplementation with chromium chloride with a significant improvement of impaired glucose tolerance; this effect was considered too small to be of clinical, therapeutic importance. A much more pronounced effect was observed in malnourished children from three of four countries studied, when trace supplementation with Cr almost immediately restored glucose tolerance to normal. Metabolic studies have suggested abnormal Cr metabolism in multiparous women, and, particularly, in insulin-requiring diabetics. The evaluation of Cr nutritional status is difficult and the requirement of man has not yet been quantified. This is due in part to unresolved problems of Cr analysis in tissues and foods with the resulting lack of reliable values. More importantly, Cr occurs in two different categories of which one (simple Cr compounds) is of little use, because it is poorly absorbed, whereas the other (Cr in certain foods) is of much greater biological value and effect. Even if a reliable analysis of total Cr in biological materials were available, it would give little information as to the proportion of the biologically active Cr in the total. GTF is labile and difficult to analyse. A tentative structure was proposed recently: Cr is believed to be co-ordinated to two nicotinic acid molecules, with the four remaining co-ordination sites protected by glycine, glutamic acid and a sulphur-containing amino acid. Synthetic compounds of this type have been shown to possess considerable GTF activity, but not to meet all the criteria previously established for GTF (Mertz, 1974*b*).

Sn. For a review, see Schwarz (1974). Sn deficiency was produced in rats raised in metal-free isolator systems and also in plastic cages outside the isolator, by feeding a purified amino acid diet which contained all the essential trace elements known at that time. Poor growth, loss of hair, lack of tonicity, and a type of seborrhoea were the prominent signs exhibited by the animals raised in the isolator, but none of these was completely prevented by a Sn supplement. However, addition of Sn compounds supplying 1–2 mg Sn/kg diet increased growth rates significantly. Stannic sulphate was the most effective compound; it resulted in growth rates 50–60% above those of the unsupplemented controls but still 40% below those of animals living in conventional cages. These results have been interpreted to indicate that Sn may be an essential trace element, but also that several then unidentified essential elements were missing from the experimental diets. The mode and site of action of Sn are unknown at present.

V. For reviews, see Hopkins (1974), Schwarz (1974). V deficiency has been induced by four independent investigators and in two animal species, the rat and the chicken.

The first sign of V deficiency in chicks, raised in the V-free isolator system and fed on a diet containing less than 10 μg V/kg, was reduced feather growth. This observation was confirmed and extended by a report of bone abnormalities in the tibia and reduced growth rates of V-deficient chicks. Deficiency signs in rats include impaired growth rates and poor reproductive performance as well as an increase of the blood packed cell volume. V deficiency, similar to excess, appears to affect lipid metabolism in an age-related fashion. Deficiency has been reported to decrease plasma cholesterol levels at an early age (2–4 weeks) and subsequently to increase them over those of supplemented controls. Plasma triglyceride levels are significantly increased in V deficiency. Deficiencies have been induced in the rat with diets containing less than 100 μg V/kg; for the chicken, a more severely deficient diet (less than 30 μg/kg) appears to be necessary. In view of the findings discussed here and of earlier ones obtained in studying the effects of pharmacological doses of V, it appears likely that this element is involved in lipid metabolism, but its site and mode of action are not yet identified.

Ni. For a review, see Nielsen (1974). Ni deficiency has been produced in three species (chicken, rat and swine) by three independent investigators. In chickens, the first reported signs of deficiency included discoloration and dermatitis of the skin, mildly enlarged hocks and thickened legs, and a change in the gross appearance of the liver. In subsequent experiments this latter finding was the most consistent, not only in chickens but also in rats. Ultrastructural changes in the liver as a consequence of Ni deficiency in both species, as well as a decrease in the oxidation of α-glycerol phosphate by Ni-deficient liver homogenates, have been described. The hepatic concentration of total lipids, phospholipids, and cholesterol was elevated in Ni-deficient chicks. In deficient rat liver a change in the ribosomal profile with a relative increase of monosomal structures has also been reported. Mild impairment of reproductive performance as well as depressed growth rates and spontaneous activity of the offspring appears to result from Ni deficiency in rats. Ni deficiency in swine has been reported to result in changes in hair, poor reproductive performance, and poor growth of the offspring. Ni, like V, appears to be involved in lipid metabolism. In addition, the consistent changes in morphology and function of the liver may lead to important clues as to the mode of action of this essential trace element.

Si. For reviews, see Carlisle (1974), Schwarz (1974). Following the demonstration in 1969 that Si accumulates in areas of calcification of growing bone, nutritional deficiency was demonstrated 3 years later in the chicken and the rat. In the former species, kept in the metal-free isolator environment, feeding with a purified amino acid diet containing approximately 1 mg Si/kg resulted in growth retardation with bone deformity, reduced strength and altered chemical composition of the long bones, flattening of cranial bones, decreased size of the comb and increased flexibility of the beak. Addition to the diet of 100 mg Si/kg as $Na_2SiO_3.9H_2O$ completely prevented these signs; the increases of growth rates in three experiments ranged from 30 to 50% over those of unsupplemented controls. In rats (dietary Si less than 5 mg/kg), Si deficiency resulted in growth retardation and changes in the

structure of the skull. Other signs, such as poor pigmentation of incisor teeth, loss of hair, seborrhoea, and loss of tonicity, also observed, were found not to be specific for Si deficiency. Growth stimulation ranging from 25 to 34% over controls was observed with the addition of 500 mg Si/kg as $Na_2SiO_3.9H_2O$, with lesser doses producing smaller effects.

Although the site and mode of action of Si have not yet been identified exactly, the observed signs of deficiency are consistent with the hypothesis that 'silicon may function as a biological cross-linking agent and contribute to architecture and resilience of connective tissue' (Schwarz, 1973).

Potential significance of the new trace elements

As mentioned earlier in this discussion, it is impossible at the present time to predict whether or not practical problems exist in animal or human nutrition with regard to any of the newer trace elements, except for Cr. Even a hypothetical treatment of such a question would have to rest on the assumptions: (1) that the experimentally determined requirement of one or more animal species is not too different from human needs; (2) that the concentrations reported in feedingstuffs and foods are valid; and (3) that the biological availability of the chemically defined compounds used in the experimental studies is representative of the availability of the elements as they occur in foods. None of these assumptions has been proven as valid; indeed several have been proven wrong for some of the newer trace elements. The formidable difficulties of Cr analysis are beginning to be appreciated after 15 years of interest in the biological role of this element. Similar problems can be expected with certainty for Sn and V. Even with Si, which occurs in concentrations 100 to 1000 times higher than those of the other new trace elements, reported values had to be revised downward following the advent of the new, more reliable analytical technique. Except for a limited amount of knowledge for Cr, nothing is known of the biological availability of the newer trace elements in different foods. Therefore, the approximate values in Table 1 are subject to serious doubt and a discussion of them is no more than tentative.

Cr analyses have indicated that certain diets, even though otherwise complete, furnish only 5 μg Cr/d, an amount barely sufficient to cover the urinary excretion of 5–10 μg/d, even if all of the Cr were completely available. The latter is clearly not so. This suggests that Cr intake of man in the United States, and perhaps in other countries, may be suboptimal. The urinary excretion of Sn and V is very low, but both elements are poorly absorbed. Thus, the adequacy of man's daily intake of these elements cannot be assessed, although it has been emphasized that many common foods contain considerably less than the 100 μg V/kg estimated to be the requirement of two animal species. Institutional diets have been estimated to contain Ni in concentrations of less than the 30 μg/kg, estimated to be the minimal requirement. The Si intake of man could vary greatly depending on his own dietary preferences. Foods of animal origin may contain considerably less and those of plant origin considerably more than the 100 mg/kg estimated to be required by animal species.

It is not known whether the reported decrease of Si with age in aortic tissue is a consequence of suboptimal intake (Garson & Kirchner, 1971).

Conclusions

Although our knowledge of the new trace elements is inadequate to arrive at health-related conclusions and although it is mainly derived from experiments conducted in a very unusual environment, the potential benefit of intensive research with these elements should not be overlooked. Deficiencies and imbalances of long-known, essential minerals occur spontaneously in animals and in man, and it is not unreasonable to assume that they may also occur for some of the new elements. Many diseases of unknown or controversial aetiology may be determined or modified by nutrition. Disturbances of glucose metabolism in the presence of normal insulin concentrations, suboptimal growth and development, altered lipid metabolism, non-infectious liver diseases, and bone and joint diseases are but a few common examples. The fact that each of these conditions can be experimentally induced by limiting the intake of one of the new trace elements constitutes no proof for the hypothesis of trace element deficiencies as causes of these diseases in man, but it should provide a challenging stimulus for future research.

Space limitations prohibit a complete tabulation of original references. These references can be obtained from the review articles cited here.

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