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Trace elements and health: an overview

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Trace element deficiencies, toxicities and imbalances in man are more difficult to relate to geochemical factors than they are in farm animals. The reasons for this are discussed and examples of such differences between man and grazing animals presented. The most convincing evidence of a geochemical causal link with human disease comes from the incidence and distribution of endemic goitre. The influence of technological developments upon this relation is discussed.

Other associations between the physical environment, including the air and drinking water, and health are given and critically examined in relation to the criteria necessary to distinguish between association and causation. The nature and extent of man-made modifications of the natural geochemical environment through technological change are discussed in relation to intakes of Fe, I, Zn, Pb and Se and their relation, in turn, to human health and disease. The currently proposed permissible limits or maximum tolerances of potentially toxic elements are presented, and the importance to these tolerances of the chemical and physical forms of the element and their metabolic interactions with other elements is emphasized.

1. INTRODUCTION

The growth, health, fertility and wellbeing of man and farm animals are known to be influenced by the amounts and proportions of the various trace elements to which they are exposed from food, drinking water and the atmosphere. The most direct relations between the geochemical environment and human health involve two halogens, F and I. High natural levels of F in potable waters in some parts of the world have long been incriminated as the cause of mottled enamel of the teeth of man and of endemic fluorosis in man and livestock. These high-F waters usually come from deep wells and bores supplied from underground sources which may be some distance away and which therefore do not necessarily reflect the F status of the soils and plants of the affected region. Endemic fluorosis thus provides a good example of a geochemical relation with human health but it is not a true 'area' problem in the way that an environmental deficiency of I can be related to the incidence of goitre, or in the way that deficiencies of Cu, Co and Se in the soils and plants of some parts of the world, affecting the health of grazing ruminants, are 'area' problems.

Trace element deficiencies and toxicities in man are more difficult to relate to the geochemical environment than they are in grazing animals for four main reasons. These are:

(i) the geographical and hence the geochemical sources of human foods and beverages are continually widening, so that the overall diet usually contains materials grown or produced on a range of soil types with differing chemical characteristics;

(ii) modern dietaries, especially in the western world, contain a wide variety of types of food, so that trace element abnormalities that may be present in one type may be offset or counteracted by the consumption of other food items with no such abnormality;

(iii) man is at the end of the food chain, so that gross soil deficiencies or toxicities affecting trace element levels in plants and in the edible tissues and fluids of animals consuming the plants will generally have been recognized and rectified earlier in the food chain in order to maintain crop and animal yields;

(iv) technological developments in agriculture, i.e. food production, and in food processing, result in gains and losses of trace elements from foods, which can erode the directness of the relation between man and his natural geochemical environment.

2. Changes in agricultural technology

Changes in agricultural practices involving technological innovations designed primarily to increase yields markedly influence the levels of trace elements in plants. For example, Zn added to superphosphate to raise cereal crop yields on extensive areas of Zn-deficient sandy soils in Western Australia, not only greatly increased yields of wheat grain per hectare, it doubled the average Zn concentration in the grain from 16 to 32 μg/g (Underwood 1962). Marked increases in the Zn content of pea seeds were later reported (Welch *et al.* 1974) when Zn sulphate was added to the culture solution in which the peas were grown. It was suggested that the nutritional value of legume seeds in respect to Zn supplies could be increased by applying Zn fertilizers 'possibly in excess of requirements for optimal plant yields'. This is an important concept in view of the marginal and conditioned Zn deficiencies that have been observed in some human populations (Sandstead 1973).

The hazards inherent in the search for ever higher yields per hectare is well exemplified by New Zealand experience. A new hybrid ryegrass was produced which greatly outyielded its parents in pasture trials. Later this hybrid was found to contain only one-fifth to one-tenth of the concentration of I of other ryegrasses grown under the same soil conditions (Johnson & Butler 1957). Where the soils were naturally high in I this had little practical significance but where they were low or marginal in I the levels of the element in the new cultivar were too low to meet the needs of grazing stock and the incidence of goitre increased. With dairy cows a further difficulty developed because the level of I in the milk reflects the I intake by the cow. Cows feeding upon the low-I ryegrass would therefore produce milk with subnormal I concentrations. This could mean the difference between an incidence of, or a freedom from, goitre in children consuming the milk and confections made from the milk, depending upon the geochemical environment.

A change in agricultural practices resulting in the opposite situation, the production of milk with abnormally high concentrations of I, has also occurred. In Tasmania, goitre in children was being controlled successfully by the use of potassium iodate in bread, in place of potassium bromate, as an 'improver' or dough conditioner (Clements *et al.* 1970). Shortly thereafter new types of I-rich antiseptics (iodophors) were introduced into certain dairies for use in milking machines, storage vats and bulk milk tankers. The I levels in the milk from areas where iodophors were used ranged from 113 to 346 μg/l, compared with only 13–23 μg/l in other areas (Connolly 1971). Comparable increases in I were found in ice-cream and confections containing dairy products. In addition, alginates made from I-rich seaweed were being used as stabilizers and thickeners in some of these confections. Some individuals were thus consuming foods artificially enriched with I from three different sources. In these circumstances a significant increase in the incidence of thyrotoxicosis was observed, mainly in older people with pre-existing goitre. We have therefore an example of technological developments resulting in excess I intakes in an area where the natural geochemical environment was subnormal in this element.

3. Changes in food technology

The refining of sugar and the milling of wheat to white flour are two of the oldest and most widespread technological processes involving food. In a recent study of the Cr content of sugar cane products from several countries (Masironi *et al.* 1973) the following mean levels were obtained: molasses, 266 ± 58; unrefined sugar, 162 ± 36; brown sugar, 64 ± 5; white sugar, 20 ± 3 μg/g. It was further pointed out that the high intake of white sugar in typical U.S. diets (120 g per person per day) not only contributes virtually no Cr, but could lead to a loss of body Cr through the Cr-depleting action of glucose (Glinsmann, *et al.* 1966). Comparable decreases in the concentrations of a range of other trace elements during the sugar-refining processes have been reported from the United Kingdom (Hamilton & Minski 1973).

In the milling of North American wheat to 72% extraction white flour the following approximate percentage losses were reported: Co, 88; Mn, 85; Zn, 78; Fe, 75; Cu, 68; Mo, 48; Cr, 40; Se, 16 (Nesheim 1974). Essentially similar figures were reported earlier by Gortner (1972). Unfortunately, data on the milling losses of potentially toxic trace elements such as Pb, Cd and Hg are much more limited but the few data that are available for Pb (Zook *et al.* 1970) and Cd (Linman *et al.* 1973) suggest that the losses in the production of white flour are smaller than those just cited for most of the essential trace elements.

Advances in food processing technology can increase as well as decrease the levels of trace elements in foods and beverages. A wide range of food additives are now employed to improve the keeping quality, colour, flavour and physical structure of processed foods. All of these additives add some trace elements and a few, such as alginates mentioned earlier, can contain large amounts of particular elements. Some additives also affect the physiological availability of certain elements. The best known of these is ascorbic acid, which increases the availability of Fe. On the other hand, another additive, the chelating agent EDTA, which is added to some prepared and processed foods to prevent oxidative damage by free metals, can markedly reduce Fe absorption in man. Cook & Monsen (1976) showed that a molar ratio of EDTA to Fe of 1:1 reduced Fe absorption in human volunteers by 28%. When this ratio was increased to 2:1, Fe absorption was reduced by approximately 50%. This effect of EDTA is believed to be due to the formation, at the low pH of the stomach, of a soluble Fe complex which is insoluble at the higher pH of the duodenum where most of the Fe absorption takes place. Since there is evidence from a number of countries that many infants and women are in a precarious position in respect to dietary Fe and exhibit a mild or marginal Fe deficiency anaemia, it is clearly important that this particular food additive should either be banned or closely controlled in all food processing techniques.

4. Human health and the environment: association or causation

Numerous links between human health and the environment, especially the soils of particular areas, have been reported, in addition to the clearly established relations involving I and goitre and F and dental health, already mentioned. For example, differential mortality from cancer of the stomach has been correlated with soil type in parts of England (Legon 1952; Smith 1960), Holland (Tromp & Diehl 1955) and New Zealand (J. J. Saunders 1960, private communication). These early studies have not identified any particular possible causal element or elements but in Finland a significant decrease in the incidence of cancer has been associated with increasing Mn content in the cultivated soils (Marjanen & Soini 1972).

Similar broad relations between the incidence of human dental caries and the nature of the soils that prevail in particular geographical areas have been demonstrated in U.S.A. (Ludwig & Bibby 1969), New Zealand (Hewat & Eastcott 1955) and in Papua – New Guinea (Barmes *et al.* 1970). In the United States and Papua – New Guinea studies, F was excluded as a primary factor in the differences observed. The situation in the primitive village communities of Papua – New Guinea is of particular interest. The mean prevalence of dental caries in 21 villages in the Sepik and Fly River regions of that country ranged from 0 to 29.5% of teeth decayed per person. Comprehensive soil and vegetable analyses from these villages correlated the caries prevalence with soil associations but attempts to identify a direct causal link with a particular element or elements were unsuccessful (Barmes *et al.* 1970). The amounts of F in the village foods were sufficient to account for the overall low frequency of caries in the areas under study but could not explain the differences among villages in caries incidence or the virtual complete freedom from caries in some villages.

There seems to me to be little doubt that the correlations or associations between the disease conditions just cited and the geochemical environment are real. But the question should be raised: 'When does a correlation or association become a causation?' What criteria should be used to claim that a particular environmental variation is a causal variation or that because A changes with B, A causes B? Hill (1965) contends that before we begin to claim causation, an association needs to be studied from the following nine criteria: strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, analogy and experiment. Strength and consistency mean, 'Is the correlation statistically high and has it been repeated by different investigators at different times?' The question of specificity needs no elaboration and temporality refers to the old cart-and-horse question: which of the associated variables comes first? Biological gradient refers to a possible dose–response curve. Does disease condition B increase as environmental factor A increases and vice versa? For example, this does happen *directly* with the severity of mottled enamel of teeth and the fluoride concentration in the drinking water. It also happens *inversely* with the incidence and severity of endemic goitre and the I concentrations of the soils and materials consumed as food.

The strongest support for a causation hypothesis comes from Hill's final criterion: experiment. It is by such means that the studies of various 'area' problems in animals have been so convincing. For example, in Cu, Co and Se deficiencies and in Cu and Mo toxicities in grazing ruminants, the relation of the disease conditions to the geochemical environment has been conclusively established by chemical analyses of feeds and animal tissues and by experiments involving supplements of the elements in question or treatments modifying the absorption, retention or utilization of those elements alone. Intervention experiments of this kind are more difficult with human populations but they are not impossible and sometimes they occur naturally, as has happened in respect to water hardness in parts of England.

In the 61 larger country boroughs studied by Crawford *et al.* (1968), the correlation coefficients between cardiovascular death rates (c.v.d.r.) during middle age and the hardness or

Ca content of the drinking water were found to be around -0.6 or -0.7 ($p < 0.001$) and were close to 50% higher in towns with very soft water than in towns with very hard water. Of particular significance was the finding that *change* in water hardness was associated with *change* in c.v.d.r. In 5 boroughs the water became harder, in 6 it became softer and in 72 it remained unchanged between 1925 and 1955. Between 1950 and 1960 the non-c.v.d.r. declined similarly and c.v.d.r. increased in all boroughs. However, in boroughs where the water became softer the increase in cardiovascular mortality was higher than average, and in those where the water had become harder this increase was lower than average (Crawford *et al.* 1971). The effect of this change in one of the environmental variables, which can be regarded as a naturally occurring intervention experiment, makes the relation between correlation and causation much more convincing.

Efforts to incriminate particular elements in the water have so far been unsuccessful, although several reports have associated the levels of Li in drinking water in certain areas with lowered annual mortality rates from atherosclerotic and ischaemic heart disease (Blackley 1969; Livingston 1970; Voors, 1969, 1970). In a more recent study of annual mortality rates from six types of cardiovascular disease among persons over 45 years of age in 24 communities in Texas (Dawson *et al.* 1978), inverse correlations were found between mortality rates and the levels of several metals, including Li, in water and in urine. Of particular interest was the finding of *negative* correlations between these rates and the ratio between the concentration of Na to that of other metals in both urine and drinking water. On the basis of their data, the authors concluded that the removal of Na from drinking water would be more beneficial than adding Li, Ca, Mg and other metals. They suggest further that (*a*) water-borne Li may contribute to the lowering of cardiovascular mortality rates by serving a diuretic function, i.e. removing excess body levels of Na, K and water; and (*b*) each alkaline metal contributes a cardiovascular mortality protective (or neutralizing) effect against Na, so that there is no single 'water factor' applying to different regions.

Although much of the above remains highly speculative at this stage, there can be little doubt that the geochemical environment as it affects the chemical composition of drinking water must be considered as a factor in human health and disease. The relative softness or hardness of the water can be important in other ways, notably with Cu and Pb, with a public health significance that remains to be evaluated.

Some years ago, a considerable increment was reported in the Cu content of soft water, compared with hard, from brook or reservoir to homes with copper piping (Schroeder *et al.* 1966). It was contended that some soft waters, with their capacity to corrode metallic Cu, could raise Cu intakes by as much as 1.4 mg/day, compared with only 0.05 mg/day from hard waters. In a more recent New Zealand study (Robinson *et al.* 1973), it was calculated that if the beverages consumed by one individual were made up with soft water from the cold tap, 0.4 mg Cu/day would be contributed from this source alone and, if from the hot tap, 0.8 mg Cu/day would be supplied from this source alone. Whether Cu intakes of this magnitude from drinking water have any deleterious effects on those consuming the water is doubtful, but it should be recognized that the amounts are considerable when related to the 1–1.5 mg Cu/day obtained from most western-style diets. Furthermore, Cu is a potent metabolic antagonist of Fe and Zn which are known to be marginal in many such diets.

The position in respect to Pb and soft water is probably more serious, at least in some areas. For example, Goldberg (1974) has shown that domestic water supplies can greatly exceed the

W.H.O. limit of safety for Pb (100 μg/l) where the water is very soft and comes from lead-lined tanks and pipes. Three groups of households in Glasgow, Scotland, where the water is very soft, were studied. They were those with (*a*) lead-lined storage tank and piping, (*b*) no tank and lead piping in excess of 20 m and (*c*) no tank and less than 20 m of lead piping. The mean Pb levels in the cold tap were (*a*) 1000, (*b*) 220 and (*c*) 100 μg/l. The mean blood levels of the inhabitants were significantly positively correlated with water Pb content. In a later study of Glasgow soft water (Moore 1977), significantly increased water Pb levels were observed even in houses with copper pipes but with lead-soldered joints. Such Pb intakes could be deleterious to the health and wellbeing of children because (*a*) children absorb Pb much more readily than adults and (*b*) this absorption is probably further increased where the children's diets are low or marginal in Fe, as they often are in poor families, if we can extrapolate from experiments with rats which have shown enhanced Pb absorption when Fe deficient (Six & Goyer 1972; Ragan 1977). Since the hardness or softness of the water is basically geochemically determined, these provide further examples of geochemical influence on trace element supplies.

5. SELENIUM AND CANCER

The whole question of a relation between the geochemical environment and human health has been given renewed stimulus by researches carried out during the last decade that have led to claims that Se protects against cancer. This, of course, is the opposite of earlier claims, based largely on dubious animal experimentation, that Se is carcinogenic. Evidence that Se is anti-carcinogenic comes from two sources: experiments with animals and epidemiological studies of human populations.

The evidence from animal experiments seems convincing as far as it goes but appears to be confined to cancers produced by certain chemicals and to the control of mammary tumours in an inbred (C_3H) strain of mice with a high natural incidence of such tumours. Schrauzer *et al.* (1976) reported a reduction of these mammary tumours in the C_3H mice over a 15 month period from 82 % in the controls to 10 % in those receiving 2 parts Se/10^6 as selenite in the drinking water. The inclusion of sub-toxic concentrations of Zn to the drinking water (200 parts/10^6 as zinc chloride) was further found to abolish the cancer-protecting effect of the Se. It was argued that the Zn was acting as a metabolic antagonist to the Se.

The epidemiological evidence began with the examination by Shamberger & Frost (1969) of human death rates from cancer in ten of the cities in U.S.A. with populations of 40000–70000 from which Allaway *et al.* (1968) had taken blood samples. They obtained a high inverse correlation ($r = 0.96$) between the blood Se levels and human cancer death rates. This relation was taken further by Shamberger *et al.* (1974) and by Schrauzer and his colleagues (Schrauzer & Ishmael 1974; Schrauzer *et al.* 1976, 1977*a*, *b*). In these latter studies, the age-adjusted cancer-mortality rates for 1960 were shown to be correlated inversely ($r = 0.47$) with the median Se levels in grains and forage crops in the United States, as reported by Kubota *et al.* (1967). When these data on Se distribution were compared with the female breast cancer mortality rates, the incidence was found to be higher in the low-Se areas than in the high-Se areas (Schrauzer & Ishmael 1974). These findings are open to possible criticism on the grounds that the data for cancer mortality rates were, of necessity, obtained on a State basis and the groupings of these States do not always conform with the areas for which the Se data were reported. There is also the pertinent question of New Zealand with its known low-Se status. No evidence of especially high breast cancer mortality has been reported from that country as would be expected from Schrauzer's findings. The position is further complicated by the recent report from Schrauzer *et al.* (1977*a*, *b*) that the apparent dietary Se intakes estimated from food consumption data in 27 countries are inversely correlated with age-corrected mortalities from cancer of the large intestine, rectum, prostate, breast, ovary and lung and with leukaemia, whereas the mortality from these forms of cancer was positively correlated with estimated individual intakes of Zn, Cu and Cd, all known Se antagonists in animal experiments.

These complex and, in the eyes of some, controversial correlations do not meet the exacting criteria of Hill, mentioned earlier in this paper in respect to causality, but they are certain to stimulate further research into the geochemical environment in relation to human cancer incidence, particularly in regard to Se and other trace elements with which it interacts metabolically.

6. PERMISSIBLE LIMITS OF THE TRACE ELEMENTS

The permissible limits or maximum tolerances of potentially toxic elements by man are, of necessity, arbitrary and must provide a wide margin of safety. Maximum tolerances cannot be demonstrated experimentally in man; they can only be inferred. Nor can they be deduced securely from experiments on animals, although these can be helpful, because of wide differences in tolerance among species. The threshold level of intake or dietary concentration, at which some adverse symptoms or physical or physiological abnormalities occur, can confidently be determined by observations of naturally occurring intakes up to known or definite toxic levels. But the next step, that is determining how far *below* such levels can be considered safe and at the same time reasonable and practicable, is difficult indeed, and forces even the most expert committees into arbitrary decisions and recommendations.

TABLE 1

	provisional tolerable weekly intake for man		acceptable daily intake for man
	mg per person	mg/kg body mass	mg/kg body mass
mercury			
total mercury	0.3	0.005	none
methyl mercury	0.2	0.0033	none
lead†	3.0	0.05	none
cadmium	0.4–0.5	0.0067–0.0083	none

† These intake levels do not apply to infants and children.

Several years ago, a joint F.A.O./W.H.O. Expert Committee produced such recommendations described cautiously as 'Provisional tolerable weekly intakes for man' for the toxic heavy metals Hg, Pb and Cd, which were considered important environmental contaminants of foods and beverages. These were expressed as in table 1 (W.H.O. 1972).

For adults consuming 400 g dry matter per day, these provisional tolerable intakes can be calculated as follows (in parts/10^6 of the total daily dry diet): total Hg, 0.11; methyl Hg, 0.08; Pb, 1.1; and Cd 0.14–0.18. These permissible dietary proportions would need to be lower for infants and children because of their higher absorption of these metals and their higher food consumption per unit of body mass.

Two points need to be made about tolerable or permissible limits of safety, quite apart from their arbitrary nature already mentioned. The toxicity of a particular intake or dietary concentration of an element depends upon the chemical form in which it is ingested and upon the extent to which other elements or compounds with which it interacts metabolically is present or absent from the diet or the environment. The importance of chemical form is particularly apparent with Hg, as is evident from table 1. Methyl Hg compounds, as they occur in fish, are better absorbed and retained by the animal body and are more toxic to the central nervous system than inorganic forms of the element.

The importance to safety or toxicity of interactions with other elements can hardly be overestimated. For example, in several animal species Se affords a high degree of protection against both inorganic and methylated forms of Hg (Underwood 1977). If these results with experimental animals can be extrapolated to man, and it seems reasonable to do so, the safe or tolerable levels of Hg would be higher where Se intakes are above normal and lower in areas of low Se status. In other words, the geochemical enviroment has both a direct and an indirect effect on the potential toxicity of dietary Hg.

Similar reasoning applies to Cd and Zn, Cd and Cu, and Cd and Fe. A given intake of Cd would be less toxic where Zn intakes are high than where they are low and, conversely, subnormal or marginal intakes of Zn which occur in some human populations would increase the toxicity or potential toxicity of a given intake of Cd. The position in respect to Cd and Fe is identical. The severe Fe deficiency anaemia characteristic of Cd toxicity in experimental animals can be prevented by Fe, or by ascorbic acid through the enhancing effect of this vitamin on Fe absorption (Fox *et al.* 1971). This suggests that persons consuming diets limited in ascorbic acid and/or Fe would exhibit increased susceptibility to the adverse effects of Cd. Their tolerable intake or permissible limit for Cd would thus be lower than that of persons consuming a diet generously provided with these nutrients. The importance of the Fe status of the diet, and by inference its ascorbic acid content, to susceptibility to Pb poisoning, and therefore to tolerable intakes of this potentially toxic metal, was mentioned earlier when considering the influence of soft water on Pb intakes.

It is apparent from the two preceding paragraphs that there is no single safe, tolerable or permissible level of intake of potentially toxic elements. There is a range or series of such dietary levels depending upon the chemical form of the element in question and the ratio that that element bears to other elements or compounds with which it interacts metabolically. It follows that investigations of the geochemical environment that focus upon a single element can be limited in value and even misleading in respect to their significance to human health and disease.

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