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The Incidence of Trace Element Deficiency Diseases

E. J. Underwood

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The incidence of trace element deficiency diseases

By E. J. Underwood, F.R.S.†

Institute of Agriculture, University of Western Australia, Nedlands, Western Australia, 6009

Introduction

On present evidence, 26 of the 90 naturally occurring elements are known to be or are claimed to be essential for animal life. These consist of 11 major elements (carbon, hydrogen, oxygen, nitrogen, sulphur, calcium, phosphorus, potassium, sodium, chlorine and magnesium) and 15 elements generally accepted as trace elements (iron, iodine, copper, manganese, zinc, cobalt, molybdenum, selenium, chromium, nickel, tin, silicon, vanadium, arsenic and fluorine). Evidence for the essentiality of the last six of these, often referred to as the 'newer' trace elements, rests largely on their effects on growth or reproduction in laboratory species maintained on highly purified diets under strictly controlled environmental conditions in which atmospheric contamination is minimized. Specific physiological functions, or involvement in vital enzyme systems, have not yet been identified for any of them except silicon, and it seems likely that the apparent essentiality of fluorine is due to a pharmacological effect in improving iron utilization in a diet only marginally deficient in iron (Tao & Suttie 1976).

It seems unlikely that these 'newer' trace elements will be found to have much practical significance in the nutrition of man or domestic animals. Naturally occurring deficiencies have not been reported for nickel, tin, silicon, vanadium, arsenic or fluorine, although the well established beneficial effects of supplementary fluoride in reducing the incidence and severity of dental caries in man could be interpreted as evidence of a dietary deficiency of that element. Such reasoning does not appear valid to me because animals can remain free from dental caries with no fluoride supplementation, and human communities exist, for instance in parts of Papua–New Guinea, where caries incidence is nil and the fluoride intakes are no higher than in other areas where the disease is rampant. It is nevertheless dangerous to assume that the newer trace elements will never be found to be of practical dietary significance, because we know so little of their functions and minimum requirements and of the factors that influence their movements through the food chain from the soil to animals and man. It is salutary to recall that the essential trace elements, selenium and chromium, were originally believed to be only of scientific interest. It is now known that a naturally occurring deficiency of selenium affecting the growth and health of domestic livestock is widespread throughout the world and that chromium deficiency is not uncommon in children and adults consuming diets high in refined carbohydrates.

† [Professor Underwood died on 19 August 1980. He had accepted an invitation to give a paper at this Meeting and had almost completed a manuscript. This was made available to the Organizers through the courtesy of his son, Dr P. Underwood. As a tribute to the work of Professor Underwood, who was an outstanding pioneer in establishing the nutritional significance of trace elements, his paper is included here by way of introduction to this record of the Discussion Meeting.]

Deficiencies of iron and iodine

Deficiencies of iron and iodine have two things in common: a much longer history than that of other trace elements and a wider and higher incidence among human populations than that of any other mineral element. In every other respect they differ markedly.

The ancient Greeks are reputed to have recognized anaemia and to have treated it by providing drinking water in which a sword had been allowed to rust. They are also said to have used burnt sponges in the treatment of human goitre. These rather picturesque procedures were of course quite empirical and nearly 2000 years were to elapse before the relation of lack of iron to the incidence of anaemia and lack of iodine to goitre were clearly established. The first suggestion that goitre might be due to a deficiency of iodine does not appear to have been made until 1830 (see Towery 1953) and between 1850 and 1854 the French botanist Chatin published his remarkable observations on the iodine levels in air, water, soils and foods in Europe from which he concluded that the incidence of goitre was associated with a deficiency of environmental iodine. Early in the last century, haemoglobin had been shown to contain iron, and the iron content of the blood of chlorotic (anaemic) women was found to be lower than that of healthy individuals (see Hahn 1937). Following these pioneer investigations, progress was rapid with both elements, and iron and iodine deficiencies in man and animals were found to be prevalent in parts of every continent and to affect millions of individuals to varying degrees. It also became clear that the aetiology of the two deficiencies is quite different. Iodine-deficiency endemic goitre is a classical 'area' disease caused primarily by lack of iodine in the soils, water and foods of the affected regions: in other words it is the environmental *source* of the foods that is crucial. Iron-deficiency anaemia, by contrast, is related primarily to the *choice* of foods and the dietary pattern of affected individuals rather than to the environmental origin of these foods. Iron deficiency is thus not an 'area' problem in the true sense of that term. The poor choice of foods that dictates its incidence, mainly in women and children, may be due to poverty, ignorance of food values, prejudices or taboos, or all three together.

Iron deficiency in grazing livestock has never been established unequivocally as a primary deficiency. In fact the pig is the only domestic species in which such a deficiency can present a serious problem. Even with the pig the problem is confined to sucking piglets maintained in concrete pens and denied the foraging of soil and grass normal to the species. By contrast, iron deficiency is probably the most prevalent mineral deficiency state affecting man, or more precisely women. Surveys in many countries have revealed a widely varying incidence of iron-deficiency anaemia and low body iron stores in women during their fertile years. Studies in England, Sweden and the U.S.A. indicate that haemoglobin levels below 11.5 g/100 ml occur in 20–25 % or more of women (see Underwood 1977), with an even higher incidence in the developing countries, where the diets contain little or no red meat, with its high iron availability, and are also low in ascorbic acid, a potent promoter of non-haem iron absorption. The profound significance of choice of foods is illustrated by a study of Venezuelan diets (Layrisse *et al.* 1974) in which the absorption of vegetal iron was doubled by the addition of 50 g meat, trebled by 100 g fish and increased fivefold by 150 g papaya containing 66 mg ascorbic acid.

As indicated earlier, the incidence of endemic goitre due to iodine deficiency is not affected similarly by dietary patterns because all the food items available and the pastures and feeds consumed by animals in the goitrous areas of the world contain subnormal iodine concentrations arising from low levels of plant-available soil iodine. The actual number of goitrous

individuals in the world was estimated 20 years ago as close to 200 million and these were present in every continent. Despite the simplicity of control measures through iodized salt or injections of iodized poppy-seed oil, goitre due to lack of environmental iodine still remains a serious public health problem in many parts of the world and may even be on the increase in some countries.

Manganese deficiency

The incidence of manganese deficiency in man and animals presents several unusual features. As with iron, a primary manganese deficiency in grazing livestock has never been reported, despite the fact that areas of manganese-deficient soils limiting crop growth occur in many countries. This is because the relative requirements of plants, in terms of tissue concentrations, are generally much higher than those of animals and even plants growing on soils low in available manganese still carry sufficient levels of this element to supply the small requirements of animals. The position is different with poultry, for which the dietary manganese requirements for growth and fertility, expressed as milligrams per kilogram of the dry diet, are about twice those of mammals. Even with this species, manganese deficiency is only likely to occur when the birds are fed on ordinary commercial rations unsupplemented with manganese and when the staple dietary grain of the birds is maize and, to a lesser extent, barley or sorghum. This situation arises because genetic differences in the manganese content of cereal grains are large and nutritionally significant even when the cereals are grown on soils supplying adequate manganese for maximum growth. Typical normal concentrations of manganese (milligrams per kilogram): maize, 5–8; barley and sorghum, 14–16; wheat and oats, 35–40. These values indicate clearly that the incidence of manganese deficiency in laying hens, with a minimum dietary manganese requirement of about 40 mg/kg, is likely to be more prevalent and severe on, for example, maize-based than wheat-based rations.

Manganese deficiency has never been observed under natural conditions in man, which again illustrates the abundance of this element in plant materials which constitute the bulk of most human diets, compared with the relatively low mammalian manganese requirement. However, one case of manganese deficiency in man has been observed resulting from the accidental omission of manganese from the mineral supplement given to a subject receiving a purified 'chemically defined' diet designed to establish the human adult requirement for vitamin K (Doisy 1974). This patient was unable to elevate his depressed prothrombin levels when given vitamin K until manganese was restored to the diet.

Cobalt deficiency

A dietary deficiency of cobalt *per se* occurs only in ruminant animals. It has never been observed or demonstrated in simple-stomached species, including man, whose needs for cobalt must be met as preformed vitamin B_{12} in the diet. A dietary deficiency of this vitamin can and does occur on all-plant rations or, as in pernicious anaemia in man, as a consequence of defective absorption, but this cannot be construed as a cobalt deficiency because the diets normally provide ample cobalt. Since vitamin B_{12} contains about 4 % cobalt and the requirement of this vitamin by adult man is about 5μg/day, it can be calculated that man's requirement for cobalt, in the form of vitamin B_{12}, is only 0.2 μg/day. All ordinary human diets contain many times this amount of cobalt.

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Cobalt deficiency in sheep and cattle occurs naturally over extensive areas in many countries, including Australia, New Zealand, Brazil, U.S.A. and the U.S.S.R. The incidence and severity of the condition varies with the degree of deficiency of cobalt in the soils and herbage of the affected areas. In its acute forms cobalt deficiency in ruminants is characterized by a severe inappetence, muscular wasting or marasmus, and anaemia followed by death, but when the deficiency is less severe the condition may appear merely as a failure to thrive or to grow or lactate normally. Under these circumstances the deficiency may be seasonal in incidence, difficult to diagnose and affected by variations in soil conditions or agronomic practices. For example, cobalt uptake by pasture plants is favoured by poor soil drainage or waterlogging (Adams & Honeysett 1964) and the introduction of high-yielding types of herbage plants to soils marginally low in cobalt can precipitate cobalt deficiency in animals dependent on the new plants. This occurs because the higher-yielding pasture species are unable to obtain sufficient cobalt to give adequate concentrations of the element in their tissues. Such a situation has recently been demonstrated with cattle on 'improved' pastures in Malaysia where cobalt deficiency had never previously appeared or been recognized. It is evident that the incidence of cobalt deficiency is determined primarily by the soil cobalt status, but is influenced considerably by the agronomic practices imposed.

Selenium deficiency

Two unusual aspects of selenium deficiency merit consideration. The first of these is the remarkable speed with which a naturally occurring deficiency in livestock in the field was recognized after the initial demonstration of the essentiality of the element in laboratory species. Within 2 years of the discovery by Schwarz & Foltz (1957) that selenium can prevent liver necrosis in rats fed on particular diets, workers in the U.S.A. and New Zealand discovered that the muscular dystrophy (white muscle disease) that occurs in lambs and calves in parts of those countries is a manifestation of selenium deficiency in the soils and herbage and can be prevented by selenium therapy. After the original field studies mentioned above, selenium-deficiency areas, in which the growth, health and fertility of animals are impaired, were found in many countries and it became apparent that the total areas of the world affected by selenium deficiency are far greater than those afflicted by selenium toxicity, the problem that initially stimulated biological interest in the element. Unfortunately, a world map showing the areas where selenium deficiency in livestock occurs naturally has not been produced.

The second unusual aspect of selenium deficiency is that it affects animals rather than plants. A deficiency of selenium in the soil does not limit plant growth or health, it simply reduces the level of the element in the tissues of the plants below the minimum required by animals consuming the plants or parts of the plants, including the seeds. With most other trace elements, including copper, zinc, manganese and molybdenum (but not iodine), subnormal levels of the element in the soil result in subnormal growth of the plants and in reduced concentrations of the element in their tissues. The extent to which one or other of these adaptations takes precedence and is significant to the grazing animal depends on the degree of deficiency in the soil, the element in question and the plant species involved.

The widespread incidence and severity of selenium deficiency in domestic livestock, including pigs and poultry for which cereal grains are staple dietary items as they are in man, has stimu-

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lated interest in the possibility of selenium deficiency in human populations. [This possibility is discussed in another contribution to this Discussion Meeting, by Diplock.] It is, however, perhaps worth noting that interactions of selenium with vitamin E and the sulphur-containing amino acids have long been recognized and dietary copper and manganese have recently been shown to interact with selenium in rats (Paynter 1980), through the presence of these metals in their respective superoxide dismutase enzymes which, like selenium in glutathione peroxidase, are involved in peroxidation pathways. Further consideration of these aspects lies outside the scope of this paper, but the incidence and nature of selenium-responsive health problems in man are clearly matters of considerable complexity in which variation in dietary selenium intakes is only one factor.

Copper deficiency

The incidence of naturally occurring copper deficiency is almost entirely confined to grazing sheep and cattle due either to subnormal levels of available copper in the soils and herbage of the affected areas or to normal or near-normal levels of copper accompanied by sufficient molybdenum plus sulphur to limit copper retention by the animal. Molybdenum can interfere with copper metabolism at dietary levels lower than 4–5 mg molybdenum/kg (Suttle 1974), and the ratio of copper to molybdenum has come to assume great significance in the incidence of hypocuprosis in sheep and cattle. The manifestations of copper deficiency, whether simple or conditioned, vary appreciably with the age, sex and species of the animal and with the severity and duration of the deficiency. As the copper available to the animal becomes insufficient for all the wide variety of metabolic processes involving this element, as a result of inadequate dietary intake, depletion of body reserves or interaction with metabolic antagonists, certain of the processes fail in the competition for the inadequate supply. In the sheep the processes of pigmentation and keratinization of wool are the first to be affected by a lowered copper status so that at certain levels of intake these but no other signs of copper deficiency are apparent. Neonatal ataxia occurs readily in lambs born to copper-deficient ewes in some areas, but rarely occurs in calves in the same areas. Further, the cardiovascular lesions affecting the major blood vessels in severely copper-deficient pigs, chicks and cattle under experimental conditions have not been observed in copper-deficient sheep. It seems that different animal species differ in their metabolic processes involving copper and that the incidence and expressions of copper deficiency are markedly influenced by its intensity, as well as by species.

Copper deficiency does not present a practical problem in pigs and poultry except when metabolic antagonists of copper such as iron, zinc and cadmium are exceptionally high. Diets containing 4–6 mg copper/kg normally provide sufficient amounts and ordinary pig and poultry rations are usually adequate in this respect. Increased rate of weight gain and improved feed efficiency in growing pigs can be obtained under certain conditions from dietary additions of copper sulphate at the very high level of 250 mg/kg, but this cannot properly be regarded as a result of overcoming copper deficiency in the conventional sense. Copper deficiency in man is similarly not a major or significant health problem even in areas where, as in parts of south-western Australia, severe copper deficiency occurs naturally in soils, herbage and grazing livestock.

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[The manuscript ended here. It is likely that Professor Underwood had intended to conclude with a survey of the role of zinc as an essential trace metal, a topic considered in detail by Professor Hambidge, Professor Hurley and Professor Vallee in their contributions to this Meeting.]

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