PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Trace Elements in Man [and Discussion]

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Trace elements in man

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[Plates 1 and 2]

It is likely that most, if not all, of the elements found to be essential in animals will be shown to be so for man, and the clinical picture produced by deficiency of the elements in the human patient will differ little from that seen in the animal, although this has been established for only five elements (I, Fe, Cu, Co and Zn). However, the link between lack of a given element in the soil and a human patient is far less direct and much more complex than that met with in the animal grazing on deficient pastures, except in isolated primitive communities. Zn is the most protean of the trace elements and has been chosen to illustrate this in human practice. Excesses of essential elements (both trace and major) give rise to toxic effects and the importance of a proper balance especially of the transitional elements in the human diet is discussed with special reference to Cu, Zn and Fe. Certain non-essential trace elements are individual and community hazards: Cd, Pb and Hg are the principal offenders for humans.

Mankind is now largely dependent on grassland products, cereals and livestock with increasing dominance of the former in human nutrition. This has reduced the bio-availability of trace elements so that study of trace metals, especially Zn and Cu, in skeletal and dental remains at human burial and occupation sites should prove useful in assessing the consequences of this striking change in dietary habits.

The last decade has seen a growing interest in trace elements in human health and disease. It was generally believed until then, by clinician and nutritionist alike, that they are so widely distributed in foodstuffs that deficiency in any element except iodine was unlikely. However, the advent of more accurate methods of assay, especially of blood and hair, and the increasing use of parenteral feeding, hitherto unsuspected trace element deficiencies have been brought to light, perhaps most dramatically with zinc. Thus, it now appears that trace metals, particularly Zn, Cu and Fe, play an important role in protein–calorie malnutrition and may be the key to Kwashiorkor. It seems likely too that the earlier age of onset of puberty accompanied by an increase in definitive adult stature, which has taken place in the developed countries over the past century, is due principally but not entirely to the greater availability of these elements and calcium in the diet.

Malnutrition is a global problem, principally affecting the developing countries and it is, perhaps, to these the biogeochemist should direct his attention, for it is there that he will find the most direct link between environment and man. It is in countries like Papau–New Guinea, with its kaleidoscopic geochemical environment, that he will find autochthonous nutrition in balanced ecosystems, as well as striking contrasts in neighbouring valleys displayed in the incidence of goitre (I), and the importance of mineral springs (Na) in the warlike activities of a tribe like the Maring, to mention but two examples. Time may be short, however, as the Papuan abandons his digging stick and, as Oomen (1971) tells us, 'could be seen sitting on a thundering tractor in the Kumbe region, now and then using his bow and arrow to shoot

a kangaroo'. Even in so-called affluent societies, the I intake is still marginal in many districts, particularly in hard-water areas, and evidence is gathering that other trace elements such as Zn and Cr may be lacking not only from the diet of the poorer sections of the community but middle classes as well.

There is no precise definition of a trace element; the term was introduced to denote the presence of an element at a time when the analytical methods available did not permit accurate measurement of its concentration in living tissues. It is difficult to demarcate trace elements from major elements, thus Fe is regarded as a major element by some workers, while others consider Mg to be a trace element. Furthermore, the classification of trace elements into essential, non-essential and toxic is both inaccurate and confusing. All of the essential elements, major and trace, are toxic in high concentrations, whereas some considered to be purely toxic, such as Se, have now been found to be essential. To be considered essential, an element must meet the criteria postulated by Cotzias as follows:

(i) the element must be present in all of the tissues of a given animal;
(ii) its concentration in a given tissue must be fairly constant from one animal to the next;
(iii) its withdrawal from the diet must lead to a specific deficiency syndrome;
(iv) the deficiency syndrome must be associated with pertinent biochemical changes;
(v) both the syndrome and the biochemical changes must be prevented or corrected by administration of the element.

Much of our knowledge of trace element deficiency states in animals has come from the laboratory, so that deficiency of several of the elements known to be essential has yet to be met with in nature. Ethical and practical considerations limit the experimental approach by the human nutritionist, as the adult volunteer on a purified diet is rarely as sensitive to micronutrient deficiency as the infant or growing child; furthermore, depletion of the element sufficient to produce clinical signs may take many months and give rise to irreversible changes, seen for example in the manganese deficient animal. Epidemiological surveys correlated with geochemical mapping are therefore of the greatest value in human practice, but it is in the clinic, either through inherited disease or the accidental omission of the element from a synthetic diet, that the human deficiency state is established or confirmed and the necessary quantitative data are obtained. Trace metal studies in man are still largely descriptive, and revision of the total body content, blood and tissue concentration of each element based on larger samples of different populations, with the use of modern analytical methods is urgently needed. Mankind is after all a polytypic as well as a polymorphic species, and each Mendelian population is more or less adapted to the environment in which it dwells.

In the brief survey that follows, attention will principally be directed to two of the essential trace elements: iodine as the element most closely linked to the geochemical environment, and zinc, as the most protean of human trace element deficiency disorders. The newer trace elements thought to be essential for animals, as well as the principal 'toxic elements' will also be dealt with.

Sources of trace elements

It is likely that most, if not all, of the 14 trace elements known to be essential for animals will be found to be so for man, and the clinical picture produced by deficiency of each element in the human patient should differ little from that seen in the animal. This has been established

for only five elements (I, Fe, Cu, Co and Zn) to date, and of these the deficiency of Co is, strictly speaking, that of a vitamin rather than a trace element because no animal can synthesize cobalamin, which cannot be obtained from any plant source other than microbial. These are derived, in common with the major nutrient elements, from the rocks, soils and waters that make up the geochemical environment that determines their distribution and availability to the plants and animals on which man depends for his sustenance. The link between the trace elements in the parent rock and the human subject is clearly less direct and more complex than that in the animal grazing on deficient pastures, with the important exception of I and F which are directly assimilated from drinking water.

The geographical sources of contemporary food and beverages in developed countries are increasingly widespread and originate from many different soil types. In addition, the average urban diet contains a variety of foods so that the deficiency of a given element in a particular plant product may be compensated for by the consumption of other foods; but this holds true for many 'primitive' societies, where monoculture does not prevail (Geertz 1963; Rappaport 1968). However, the changeover from household to factory production of foods on a large scale which followed World War II, and involves the processing, preservation and packing of foods, tends to reduce the availability of trace elements to the consumer. This means that market garden products, usually local in origin, and therefore dependent on local geochemical conditions, may again become important in providing adequate trace element contributions to the diet, even though they are seasonal.

The milling of cereal grains result in loss of essential trace metals, especially Zn, Fe and Cu. However, the reduction of fibre and phytate which milling involves partly compensate for this loss by increasing the availability of the elements remaining in the flour as these would otherwise be lost in the faeces through binding to fibre or chelation by phytate. The refinement of sugar results in a marked reduction of all the mineral elements, especially Cr as Professor Underwood has indicated in this symposium, but this too may provide calories without adding to the fibre in the diet.

The plant breeder, in his efforts to improve the nutritional properties of the staple cereals with respect to proteins and calories, has tended to neglect trace metals, and intensive animal breeding has already led to trace metal deficiency in the United States.

Evolution and prehistory of hominid diet

Man has slowly evolved from primate ancestors who lived at the fringes of the tropical forests about 3 million years ago, where they consumed an ominivorous but principally vegetarian diet. Some of the early hominids took to the life of a predator on the herbivores grazing on the savannah and grasslands which had gradually encroached on the forests as a result of climatic changes. In doing so he exploited his erect posture and bipedal gait, which released his hands for carriage of food and implements which he began to fashion. Later he exploited fire for hunting and for storing and cooking meats (Lee & Devore 1969). Cooked foods had important effects on his facial structure and dentition which are still operating, well demonstrated by the fate of the wisdom tooth and lateral incisors. Throughout the Palaeolithic, meat figured more or less prominently in his diet, and provided essential nutrients in quantities adequate for growth and reproduction, in contrast with plant sources. Indeed, to give but one example, the small child cannot consume enough maize to satisfy his needs for growth and development,

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

without protein from other sources, whereas the grown adult can do so, to fulfil his protein needs (Newman 1975).

With the advent of agriculture 15 000 years ago, cereals derived from a few wild grass ancestors have increasingly dominated the human diet and it could be said that mankind is attempting to revert to the predominantly vegetarian diet of his distant ancestors. It seems clear that for protein and essential trace element needs, modern man is not well adapted to an almost exclusively vegetable diet and that 500 generations have not sufficed to cope with this remarkable dietary change.

Geochemistry and palaeo-nutrition

Archaeologists in the United States and Europe have begun to investigate the interrelations between diet, disease and the environment: this involves a multi-disciplinary approach in which geochemistry plays a fundamental role.

The pioneer studies of Indian habitation sites in the Kentucky blue grass area, by Louise Robbins (1977) and her colleagues, indicate that trace minerals may be the key link in the life of the populations concerned. She points out that 'while the blue-grass of Kentucky may be a superior food for race-horses today, during pre-historic times the soil apparently lacked some necessary nutrient. Animals avoided the area because of the scarce food sources, and pre-historic people follow their own food base the animals'. With the introduction of agriculture, a sedentary population was established but deficiency of minerals in these soils, especially Zn and Mn, with maize an important, if not the staple, source of food, produced significant changes in the health of the people, evidenced by the increase in dental and skeletal pathology found in the human remains.

Malnutrition is rare in the Mbuti pygmies, who are adapted to the life of hunter–gatherer in the Ituri forest, but promptly followed the displacement of other pygmies in nearby Ruanda, as forests were cleared for tea and coffee plantations (Turnbull 1976; Cavalli-Sforza 1977).

Bones and teeth lend themselves to non-destructive trace element analysis and four of these, Zn, Cu, Mg and Sr, are present in sufficient quantity to be useful indicators of the diet consumed by the relevant population. Indeed, it may be possible, under favourable conditions, to deduce the social stratification which obtained in certain communities. The Zn content of bone is useful in assessing the proportion of meat to that of vegetables, predominantly cereals, reflected in the Mg content, in the diet, and this can in turn be correlated with the stature and degree of mineralization of the bones of mature individuals in the population, so that the changes that accompany transition from a principally carnivorous to a vegetarian diet can be followed over several generations. Reduction in the Cu content of the skeletal remains may reflect the availability of the element, and the Sr present may be helpful with respect to vegetables (Gilbert 1977).

Studies such as these will be undertaken as trace metal analyses become routine clinical procedures. These may reveal the effects of dietary changes on European and other communities during the past several centuries, and help to modify or corroborate the conclusions of historians such as Duby, Lebrun, Le Roy Ladurie and the *Annales* school of historiography with its emphasis on the ecosystem, as well as the economic historian in determining the subsistence levels of worker and peasant in recent centuries.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Factors influencing the availability of trace elements

The principal factors which influence the availability of trace elements are shown in table 1, but the presence of a given element in the soil, plant or ingested food does not ensure that adequate amounts will be absorbed.

Table 1. Factors affecting availability of trace elements

soil type	plant	animal	food	diet	
sandy	leaf	milk	(*a*) raw	fibre	parasites
(leaching of elements)	stem	egg	(*b*) cooked	phytate	worms
sandstone	root	meat	steamed	Ca	malaria
	grain	(*a*) red	boiled		
		(*b*) white	roast	Zn	infection
			smoked		gut
limestone	nut	liver		Fe	systemic
(resistance to erosion)	fruit	kidney		Cu	

We are still largely ignorant of the mechanisms whereby a trace element gains access to its target. We do not know the molecules responsible for absorption and transfer across cell membranes, those within the cell as well as in the plasma, and we know little concerning the ligands which may assist or hinder these activities, during digestion or after assimilation.

Trace element interactions

It is almost certain that most trace elements operate biologically as metal chelates and a consideration of the coordination chemistry of the cationic element led Hill & Matrone (1970) to appreciate the possible significance of electrons in the d shell of the ion, as most of the essential elements are found in the first transition group. They propose that elements that resemble each other physicochemically (in their electronic structure) will tend to act as biological antagonists. This rule appears to be generally obeyed, especially by Zn, Cu and Fe which must be in proper balance if serious deficiency of one or more of the elements not in excess is to be avoided. Thus a patient with coeliac disease, who was known to be deficient in Zn but whose lack of Cu was not suspected at the time, began to take large doses of Zn supplements which brought her disease under control, but she subsequently developed severe anaemia.

Iodine

I deficiency is a very important global health problem with an estimated 200 million persons affected by goitre, hypothyroidism or endemic cretinism and its associated deaf mutism. Goitre is the name given to the swelling of the thyroid gland in the neck (figure 1, plate 1), which follows when the intake of the element is consistently less than 50 mg per day. The thyroid gland normally synthesizes two important iodine-containing hormones, thyroxine (T4) and triiodothyronine (T3). Reduced intake of I produces reduced synthesis of T4, which in turn leads to an increase in the secretion of the thyroid stimulating hormone of the pituitary. This causes the thyroid to take up more I as well as producing the goitrous swelling. Goitre may appear at any age in an endemic area and in districts of high endemicity, neonatal goitre is a

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

good index of the degree of I deficiency in the geochemical environment. In regions where the deficiency of the element is less marked, although visible swelling of the gland may be evident in the pre-pubertal child, it is in the adolescent of both sexes that goitrous swellings usually appear, no doubt because of the increased need of the hormone for the adolescent spurt growth as well as the physiological changes which accompany puberty. These changes occur in girls between 12 and 18 years but somewhat earlier in boys because of their greater physical activity.

It is rare for a goitre to develop in adult males living in endemic areas, if swelling of the gland has not appeared in childhood or adolescence, but it is not all uncommon for goitres to appear in women for the first time during pregnancy, and Lawson Tait, just over a century ago, drew attention to the fact that each succeeding pregnancy is often followed by further enlargement of the gland.

Sequelae of goitre in adults

Goitres often disappear in adult males, but it is rare for this to happen in women, particularly those who become pregnant. Women are more likely to develop nodular goitre and in some endemic regions these may be of enormous size, e.g. in New Guinea and Indonesia, where they figure in puppets. Myxoedema or hypothyroidism may follow degenerative changes in the nodule, and usually affect women at the menopause or later. Thyrotoxicosis (Grave's disease) is more frequent in some endemic areas, but it is not clear why this is so.

Endemic cretinism

The cretin appears normal at birth, but signs of mental and physical retardation are seen when the infant is about 6 months old, leading ultimately to the characteristic facies with a large head, the delay in walking until the 6th or 7th year, lack of speech and the characteristics lordosis and stance (figure 2, plate 1). The face is vacant with the tongue characteristically large, protuding between the teeth. Deaf mutism is a feature of cretinism and is prevalent in those areas where iodine deficiency is most severe.

Incidence of goitre in the British Isles

Goitre was moderately prevalent even in southeast England, between the wars; during World War II a high incidence of goitre was found in young women called up for work in the factories, and it was estimated that as many as half a million may have been affected in England and Wales alone. Even as recently as 1958, it was found that the incidence of goitre had increased from 26.9 to 44% in schoolgirls in the attractive Coltswold country overlying a belt of limestone, compared with the survey of the same schools in 1948, whereas that in the boys remained at 14.8%. Goitre is less prevalent in Scotland where the I levels of the softer waters suffice to prevent goitre, but these are the waters associated with a higher incidence of cardiovascular disease. In Ireland the advantages of close proximity to the sea are displayed in the absence of goitre from Galway and Kerry, where consumption of sea food ensures a high I intake. However, higher I intake is not without its disadvantages: in Iceland, which is a high I area, hyperthyroidism is common, and papillary cancers of the thyroid gland are five times commoner there than in Scotland. Follicular cancer of the thyroid gland appears to be the malignancy associated with endemic goitre in I-deficient areas.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

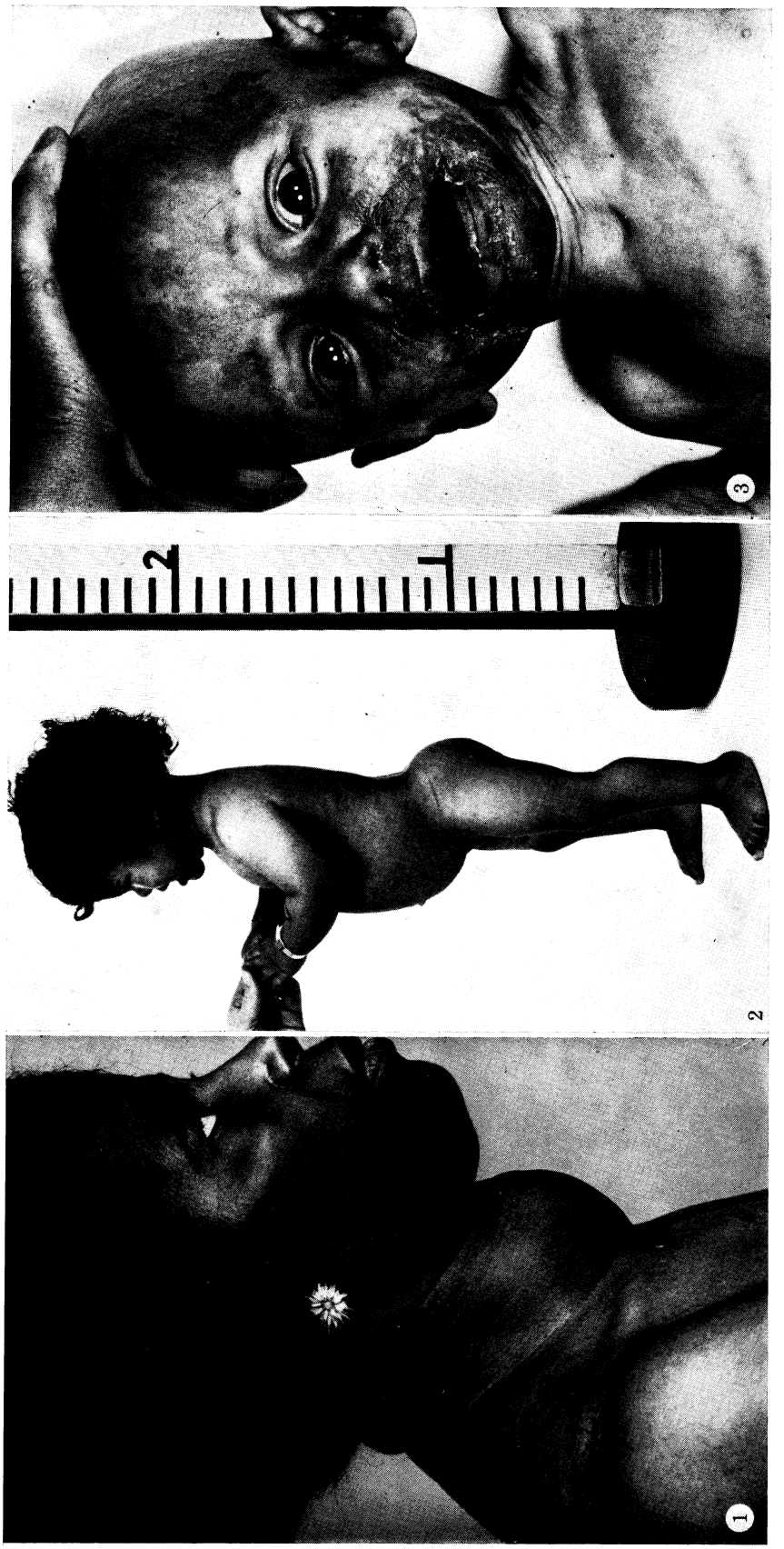

FIGURE 1. Goitre, typical.

FIGURE 2. Cretin, showing characteristic stance, short stature and delay in walking.

FIGURE 3. Acrodermatitis enteropathica, showing eruption around mouth, nose and ears. Severe zinc depletion will produce identical changes.

(*Facing p.* 70)

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

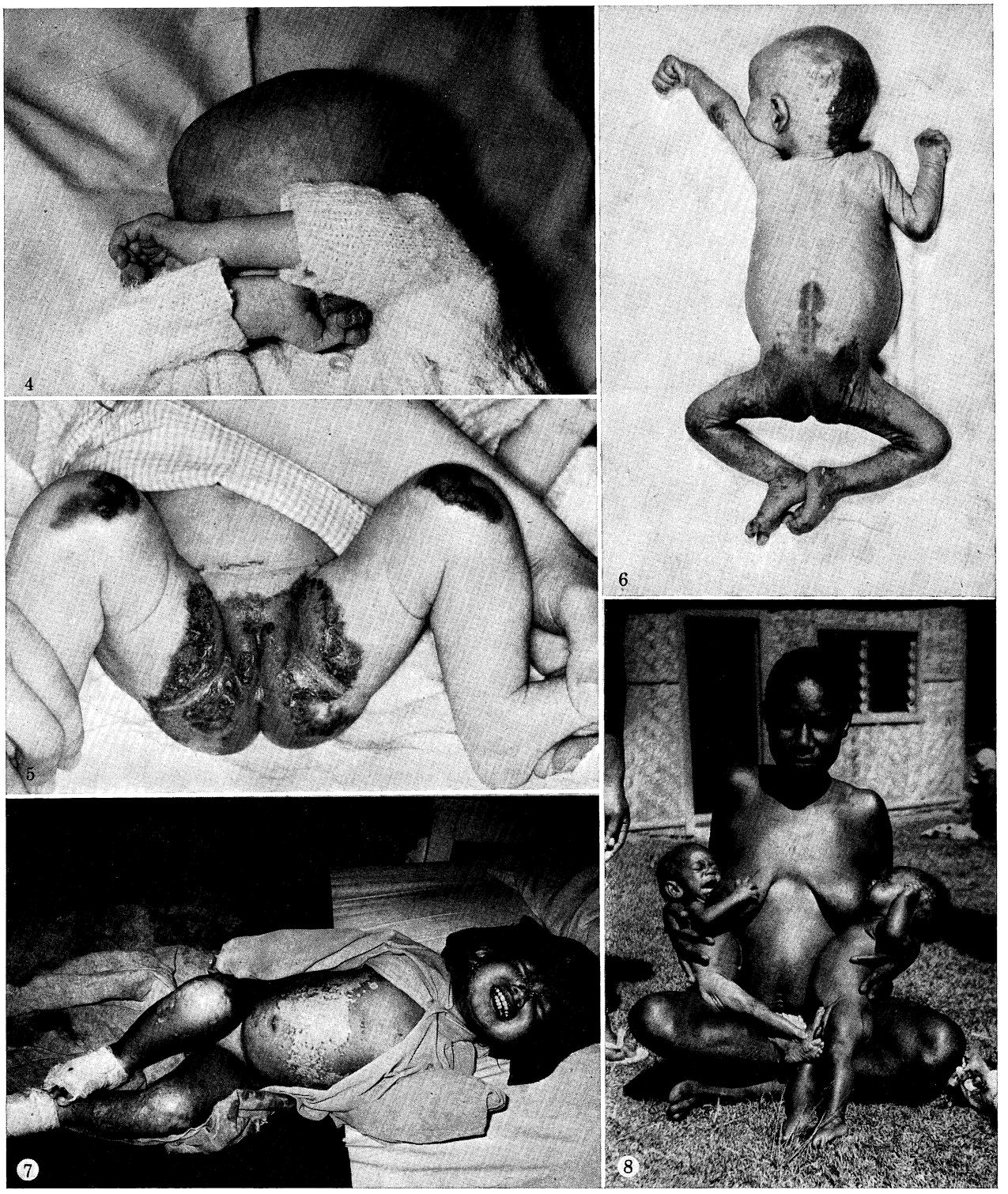

FIGURE 4. Photophobia in acrodermatitis enteropathica; note also paronychia affecting all of the digits from each of which the nail has been shed.

FIGURE 5. Exudative and scaling eruption affecting the external genitalia and buttocks, with blistering and scaling on the knees.

FIGURE 6. Psoriasiform plaques affecting skin over bony prominences; note also total alopecia and paronychiae.

FIGURE 7. Skin changes in Kwashiorkor, with generalized hypopigmentation, scaling and inflammation of skin of abdomen and knees.

FIGURE 8. Genesis of Kwashiorkor: the male twin is better nourished than his sister who is a candidate for Kwashiorkor should she survive to be weaned.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Iron

Fe is one of the commonest elements in the Earth's crust, yet most forms of life are unable to absorb or utilize most of the element present in the environment. All mammals will reject Fe, even when present in a biologically acceptable form, if the animal does not need it, and will only permit its absorption to deal with Fe losses. The absorption of Fe is permitted or increased in response to the latter, and once absorbed the element is carefully conserved. Unlike other trace metals, Fe which is no longer needed is not excreted and accumulates especially in the liver in conditions of Fe overload. Fe is lost only through desquamation of the skin and other surface epithelia and through bleeding. It is therefore not surprising that women in the reproductive epoch are particularly vulnerable to Fe deficiency which leads to anaemia, which is by far the most important trace metal deficiency in the World at the present time. This is less a geochemical problem and is almost entirely attributable to improper or inadequate diet, even in the so-called affluent society. Pregnancy and lactation increase the demand for Fe, which is also needed for growth in childhood, and these represent vulnerable phases in the development of the individual.

Infection and parasitism, especially malaria and worm infestation, aggravate the deficiency in the Third World, and may themselves be responsible for the anaemia.

Fe overload, due either to excessive ingestion of the element seen in Bantu siderosis, or in haemochromatosis, an inherited disorder, leads to congestive failure, hypoganodism with testicular atrophy in the male and amenorrhoea in the female, as well as characteristic skin pigmentation.

Geophagia

The practice of geophagia or eating of clay or soils may be of interest to the geochemist. It has been attributed to lack of Fe in the diet as it was thought that the individual seeks to replace the missing element by consuming the soil. It was a prominent feature of the hypogonadal male dwarfs with anaemia and Zn deficiency in the Middle East and pica has also been reported in Zn deficient children in the United States. Pica, of course, is often responsible for chronic Pb intoxication in children. However, studies of Fe absorption in Turkish women with geophagia indicate that eating clay may itself be responsible for, rather than a consequence of, the Fe deficiency (Underwood 1977). The humus in the soil is rich in ligands which chelate Fe and some bind Fe and make it unavailable.

Copper

The total body content of this element is approximately 0.1 g and the daily needs have been estimated to be about 2 mg for the average healthy male. Copper deficiency, leading to severe anaemia and neutropenia, principally affects premature and small babies who may therefore be particularly vulnerable in Cu deficient areas. Unlike Zn, there is no inherited disorder of Cu metabolism attributable to a simple deficiency; it is true that Menkes kinky hair syndrome (Danks *et al.* 1972), with its low Cu and caeruloplasmin resembles Cu deficiency in sheep, and does not respond to copper supplements, contrasting with the prompt response of patients with acrodermatitis enteropathica to Zn. Depigmentation of the hair, which is a feature of Kwashiorkor, may be a manifestation of Cu deficiency, and in this respect the occurrence

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

of periodic banding of the hair, met with in Kwashiorkor in Central America, may reflect changes in the availability of the element, possibly associated with the local geochemistry.

Wilson's disease, inherited as an autosomal recessive trait, is characterized by life-long deficiency of caeruloplasmin and an excess of Cu in the liver. This leads to the retention of Cu amounting to 1 % of the diet intake per year, which continues throughout the life of the patient; Cu also accumulates in the brain and kidney, leading to the death of the patient through liver failure or other causes.

Zinc

Zn is second only to Fe among the essential trace elements with a total body content of between 2 and 3 g in the average adult, and a daily requirement of 15 mg. Although a transition element, it differs in having only one oxidation state and no unfilled levels in the valency shell of the ion, which may account for its presence at the active site or in close association with no fewer than 90 mammalian enzymes of differing activities. It is therefore not surprising that manifestations of deficiency of the element are so protean. Zn deficiency was first suspected in the early 1960s (Prasad *et al.* 1961, 1963) in male dwarfs from the rural districts around Shiraz in Iran, who presented with an unusual syndrome comprising hypogonadism, dwarfism, hepatosplenomegaly, anaemia and geophagia in the absence of any cause for Fe deficiency, such as worm infestation. However, the finding of low plasma Zn levels in apparently unaffected males from this and other regions of the Middle East was held by some to rule out Zn deficiency as the cause of the syndrome, and it was not until 1973 that Zn deficiency was conclusively demonstrated in an infant suffering from acrodermatitis enteropathica (Moynahan 1973; Barnes & Moynahan 1973; Moynahan 1974).

Acrodermatitis enteropathica is a rare inherited disorder, transmitted as an autosomal dominant trait, which presents when the infant is weaned, or earlier in the bottle fed baby, with a striking constellation of symptoms affecting the skin, with moist eczematous and scaling lesions round the natural orifices of the body (figure 3, plate 1; figure 5, plate 2) psoriasiform plaques then develop over the bony prominences of the body (figure 6, plate 2), the nails are shed from all of the digits which become the site of a bloody paronychia (figure 4, plate 2) and the hair is progressively lost, leading to total alopecia (figure 6). These changes are accompanied by disturbance in bowel function, characterized by the passage of pale, bulky foaming, stinking stools, at first intermittent but later continuous. There is a profound disturbance in mood and visual behaviour, evident from the onset of the disorder: the small patient is tearful, irritable and withdrawn. He resents any interference associated with feeding, bathing, napkin changing or dressing and he is difficult to console, failing to respond to the close contact and petting which relieves most distressed infants. Smiling is lost; indeed its return is the earliest sign that the disorder has been brought under control. Photophobia is prominent (figure 4), but there is a remarkable disturbance in visual behaviour, concomitant with the change in mood, consisting of marked gaze aversion and avoidance of eye-to-eye contact. The child views the world suspiciously and surreptitiously through sidelong glances with head and eyes downcast. Similar changes may be seen in infants and young children suffering from various malabsorptive disorders, and the behaviour of the child with Kwashiorkor is so like that of the Zn-deficient or Zn-depleted child (Moynahan 1976) who also exhibits the combined immunoincompetence which led to early death in acrodermatitis enteropathica, suggesting that Zn may be the most important but not the only factor, which converts marasmic

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

protein-calorie malnutrition into the more lethal Kwashiorkor (see figures 7 and 8, plate 2, for illustrations of Kwashiorkor).

Early studies at the Hospital for Sick Children led me to suspect that the protein in the diet must in some way be associated with the disorder, because complete remission follows when breast milk, but not cow's milk, is the sole source of protein in the diet. In the early 1960s, trace metal deficiencies were thought to be improbable. Failure of a baby girl of Italian parentage to respond to Diodoquin – a derivative of the versatile chelating agent 8-hydroxyquinoline which had been successful in producing remission in other cases – whose symptoms were considerably worsened, when she was given breast milk, led to the recognition of the lactose intolerant variant of the disease which is met with in populations with a high incidence of adult lactose intolerance (Moynahan & Clayton 1966; Moynahan 1966). The baby thrived on a synthetic lactose-free and sugar-free medication. Two children of Iranian and Armenian parentage, as well as a cousin of the Italian girl, responded well to the same régime. However, the younger sister of our original patient failed to do so, and also to a variety of synthetic diets and medicaments. The finding of low plasma Zn levels led us to give Zn supplements with immediate benefit, only to be followed by prompt relapse when they were withdrawn. Her speedy recovery when Zn was given again indicated that it might be fundamental to the pathogenesis of the disease, a hypothesis soon confirmed in the remaining eight patients under my care by withdrawal of the drug and replacement with Zn supplements alone (Moynahan 1973, 1974).

The manifestations of Zn deficiency in adults may range from simple loss of taste and appetite, a mild persistent psoriasiform rash, loss of libido, to a condition identical with that seen in the child with the natural disease. A striking example of this followed treatment with penicillamine and it is of some interest that it was the patient's father, a farmer, who recognized that his son had symptoms closely resembling Zn deficiencies in pigs, that led to the identification of the cause of his son's condition (Prasad 1976). Zn deficiency, as well as the malabsorptive states already mentioned, was soon recognized in patients on parenteral feeding (Bos *et al.* 1977).

Low serum Zn levels in pregnancy appear to be associated with increased risk of prematurity and low birth mass in the baby as well as prolonged labour and increased blood loss in the mother (Jameson 1976). Cigarette smoking during pregnancy carries identical risks and it is tempting to suggest that the element may be chelated by metabolites of nicotine, thereby reducing its availability to the growing foetus.

Essential trace element deficiencies awaiting confirmation in man

Fluorine

Although F appears to be essential for dental health, well demonstrated by the prevention of caries in children's teeth when drinking water is fluorinated, it is not clear whether this is due to a direct action on the microbes responsible for tooth decay on the surface of the tooth, rather than incorporation into the enamel itself. Tea appears to be rich in F and it has been asserted that the tea drinker is assured of an adequate intake of the element. The role of F in bone metabolism is disputed: it has been suggested that it promotes mineralization and inhibits resorption of bone. Therefore, the finding that osteoporosis is less frequent in high F areas of the United States may have an important clinical bearing and should stimulate further research into the metabolism of the element in humans.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Excess of the element (fluorosis), leading to mottling of the teeth, with chalky white patches which then become stained yellow or brown, is not uncommon in many parts of the world. The severity of these changes is dependent on the F content of the water as well as the amount consumed by the individual. The skeleton as well as the teeth is involved in severe fluorosis, met with in South Africa and Southern India, which leads to osteoporosis, osteosclerosis with calcification of the ligaments and tendons, and crippling deformity in middle life. The widespread occurrence of knock knees in adolescents and young adults in areas of endemic fluorosis in Southern India, is of interest. It is principally confined to the poor, whose staple food is sorghum and whose diet is low in Ca but high in Mo (Underwood 1977).

Selenium

Soon after the discovery that the element is essential for rats, Se deficiency states were recognized in livestock, but human deficiency has not yet been reported. It is likely, however, that the essentiality will be confirmed before long, particularly as it is a constituent of the enzyme glutathione peroxidase which plays a prominent role in dealing with free radicals and the preservation of the integrity of biological membranes. Se is intimately related to, but independent of, vitamin E in the animal economy, and may to some extent compensate for the lack of the vitamin. Both possess antioxidant properties which may be of considerable pathological significance. The discovery that Se will protect animals against the toxic action of

TABLE 2. CONFIRMED HUMAN TRACE ELEMENT DEFICIENCIES

element	amount in adult/g	recommended daily intake, adult male mg	source in diet	major biological role	deficiency	excess
Fe	4–5	10	eggs, meat, whole grains, green, leafy vegetables	haemoglobin (oxygen carrier), cytochromes myoglobin (energy production)	microcytic anaemia	haemochromatosis and siderosis (Bantu)
Zn	2	15	present in most foods (but not always available); shell fish, meat (esp. red), liver	essential for cell division and protein synthesis, euthymia	early death (thymic hypoplasia), failure to thrive in infants and young children, delayed puberty, retarded growth, short stature, pregnancy wastage	nausea, vomiting, fever
Cu	0.1	2	meats, liver, water	closely linked with iron metabolism, monamine oxidases	anaemia	Wilson's disease
I	0.011	0.14	sea food, dairy produce, many vegetables (soil dependent)	thyroid hormones, essential for cell metabolism	goitre and cretinism	excess may lead to goitre
Co	0.0015	vitamin B_{12}	meats, liver, milk	corrin ring in vitamin B_{12}	pernicious anaemia	industrial risk

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

inorganic and organic Hg compounds, coupled with the finding of high concentration in marine animals, with high mercury Hg burdens, and a 1:1 accumulation of Se and Hg in Hg miners suggests that the element may be essential as a detoxicant.

The level in food is closely related to that in the soil, so that geochemical studies may help to elucidate its role in human health; the more so because as epidemiological studies from the United States suggest that the mortality from cancer of the stomach, oesophagus and rectum tends to be higher in low Se areas and this seems to be so for cancer of breast in women as well. Remarkable reduction in morbidity and mortality from cardiomyopathy has followed Se supplementation in China (see note added in proof).

Chromium

Severe Cr deficiency has been produced during the course of long-term parenteral nutrition, in which peripheral neuropathy was associated with impaired glucose intolerance, and is not uncommon in the elderly, some of whom may improve with Cr supplements. The finding of regional variations in the concentration of Cr in the liver and kidney in different geographical regions of the United States is of considerable geochemical interest (Underwood 1977).

Manganese

Mn deficiency has been observed in association with vitamin K deficiency in a single volunteer in whom the element was accidentally omitted from the test diet. Mn activates glycosyl tranferase in the synthesis of glycoprotein and polysaccharides. Children appear to require larger amounts of the element, which suggests that it may be essential for growth, but this remains to be established. Mn deficient soils in Finland have been associated with an increased incidence of cancer.

Molybdenum

Mo, like Mn, is found in all the tissues and fluids of the body with little difference in concentration in any particular organ. It is a constituent of several enzymes, e.g. xanthine oxidase associated with purine metabolism, and an increased incidence of gout has been found in areas of Soviet Armenia where there is a high content of Mo in the soil (Kovalsky, this symposium).

Toxic trace elements

Certain elements that are toxic in very small amounts have become serious environmental hazards for plant, animal and man alike. The risks are usually local and often confined to the vicinity of a smelter or other industrial plant, but these and abandoned mine workings may contaminate the soil and water supplies for a number of years, with adverse effects on the population, including an increase in the incidence of cancer and other diseases. Fears have also been expressed concerning the long term global effects of the accumulation of heavy metals such as Pb and Hg in the environment; Cd and As are also important anthropogenic hazards.

Sources of toxic elements

Although the eating of a toxic element is the principal hazard for man, other and more direct routes may be followed. The toxic element may be inhaled in the smoke, dust or fumes produced during mineral extraction, smelting and processing, while the combustion of fossil fuels adds steadily to the environmental burden of Pb, Hg and As. Contamination of wells and streams

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

may affect drinking water, but consumption of fish and shellfish that have ingested the element is more often responsible for epidemic outbreaks of poisoning. Food plants may be contaminated by dusts or sprays employed to prevent fungal or other infections and to deal with ectoparasites. Serious epidemics have followed the consumption of seed corn, impregnated with organic mercurials, used to make flour.

Cadmium

Cd is toxic by whatever route it is administered and some of the changes produced may result from its metabolic antagonism to Cu, Zn and Fe: these include anaemia and skin changes. It will induce hypertension in animals but this is not a feature of human Cd poisoning, although hypertensive patients accumulate the element in the kidney and excrete more in the urine. It is possible that Cd, by reducing the availability of Zn to the foetus of mothers who are heavy cigarette smokers and whose Zn status may be marginal, may add to the risk of prematurity, low birth mass and other obstetric complications. Cd may be completely lacking from the newborn and cannot therefore be essential, nor is it secreted into milk. The body content of Cd steadily increases with age, accumulating mainly in the liver and kidneys where it is sequestered by metallothionein.

Arsenic

Arsenic is ubiquitous and all foodstuffs contain small amounts of the element, where it is found in the very much less toxic pentavalent form. Arsenic has a particular affinity for keratinized tissues and is continuously shed in hair, nails and skin. Arsenical contamination of the environment is decreasing. Chronic intoxication produces a characteristic pigmentation of the skin associated with warty growths and malignancies in the skin and internal organs. Diarrhoea and vomiting are features of acute poisoning by inorganic arsenical salts. Organic arsenicals, which were the mainstay of the treatment of syphilis before penicillin, gave rise to a vast array of toxic and allergic complications.

Mercury

Hg is a ubiquitous element found in appreciable quantities in over 30 common minerals; well defined zones bearing the metal have been identified, and it is of interest that oceanic ridges are numbered among these, in view of the high content of the element in the tissues of deep-sea fish and their avian and mammalian predators. There is a well established biogeochemical cycle with microbes playing a fundamental role in the degradation and synthesis of organic mercurials. Hg is released from combustion of fossil fuels and the Hg content of the atmosphere is thought to be increased through release of Hg vapour consequent on excavation, but volcanic and other natural agencies probably contribute more from this source.

Toxic effects vary with the compound concerned; Hg vapour may be inhaled or the element may enter the food chain as an organic mercurial such as methyl mercury or more directly through ingestion from contaminated fingers. This was responsible for a recent small outbreak which affected the detectives in a provincial constabulary. The affected officers had used an organic mercurial for finger-printing suspects and showed symptoms of erythrism. Chronic intoxication with Hg gives rise to gingivitis, tremors and personality changes (shyness and blushing), hence erythriasm, as well as albuminuria. Ingestion of mercurial salts produces severe diarrhoea and toxicity. Of the organic compound, alkyl derivatives are the most toxic,

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

with methyl Hg, which was responsible for Minimata disease in Japan, among the more important.

Alkyl mercurials are rapidly absorbed from the intestine and through the skin and give rise to serious permanent damage to the central nervous system, including mental impairment.

Certain bacteria methylate Hg and, with demethylating organisms, play a key role in the Hg cycle but have not been incriminated in any outbreak.

The finding that Se compounds are antagonistic to inorganic and organic mercurials in animals, not only holds promise of effective treatment and prevention of intoxication by mercurials, but suggests a possible essential function for Se as a detoxicating agent.

Lead

Pb had long been recognized as an industrial hazard before it was appreciated that house dust is a prolific source of the element from paint, the street, old batteries, solder from cans and toothpaste tubes. Pica in children who eat paint or plaster is a common cause of Pb poisoning.

Pb impedes the synthesis of haem and accumulates within the red cells as well as the bones to give rise to anaemia, headache and dizziness. Wrist drop and colic in adults as well as encephalopathy in children are also features of chronic Pb poisoning.

The newest trace elements

The introduction of the plastic isolator technique has led rapidly to the recognition of five further elements as essential in animals. These deserve brief mention although their physiological roles are not fully established and they do not yet fulfill all of Cotzias's postulates.

It is now clear that F is essential for growth in the rat and that there is progressive infertility and delayed onset of sexual maturity in mice as well. Si appears to be essential for initiating mineralization of bone, where it seems to function as a cross-linking agent in certain mucopolysaccharides and different collagens. Deficiency in V leads to impaired growth and poor bone development in chicks as well as diminished reproductive performance in rats. It may play an important role in the regulation of cholesterol and plasma triglyceride levels, of current interest in cardiovascular pathology. Chicks, rats and pigs deficient in Ni impaired growth and Sn has been shown to be essential for growth in rats.

Note added in proof (26 *July* 1979). It has just been reported from China that low levels of Se were found in the hair of persons of all ages in certain provinces in which there is a high incidence of cardiomyopathy. 36603 persons were given daily supplements ($\frac{1}{2}$–1 mg) of Se, with a striking reduction both in morbidity (21 cases) and mortality (3 cases) when compared with 9642 individuals, of whom 107 developed a heart condition and 53 died.

I am grateful to Mr John Maynard, Curator of the Gordon Museum, Guy's Hospital and Medical School, for permission to reproduce figures 1, 2, 7 and 8.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

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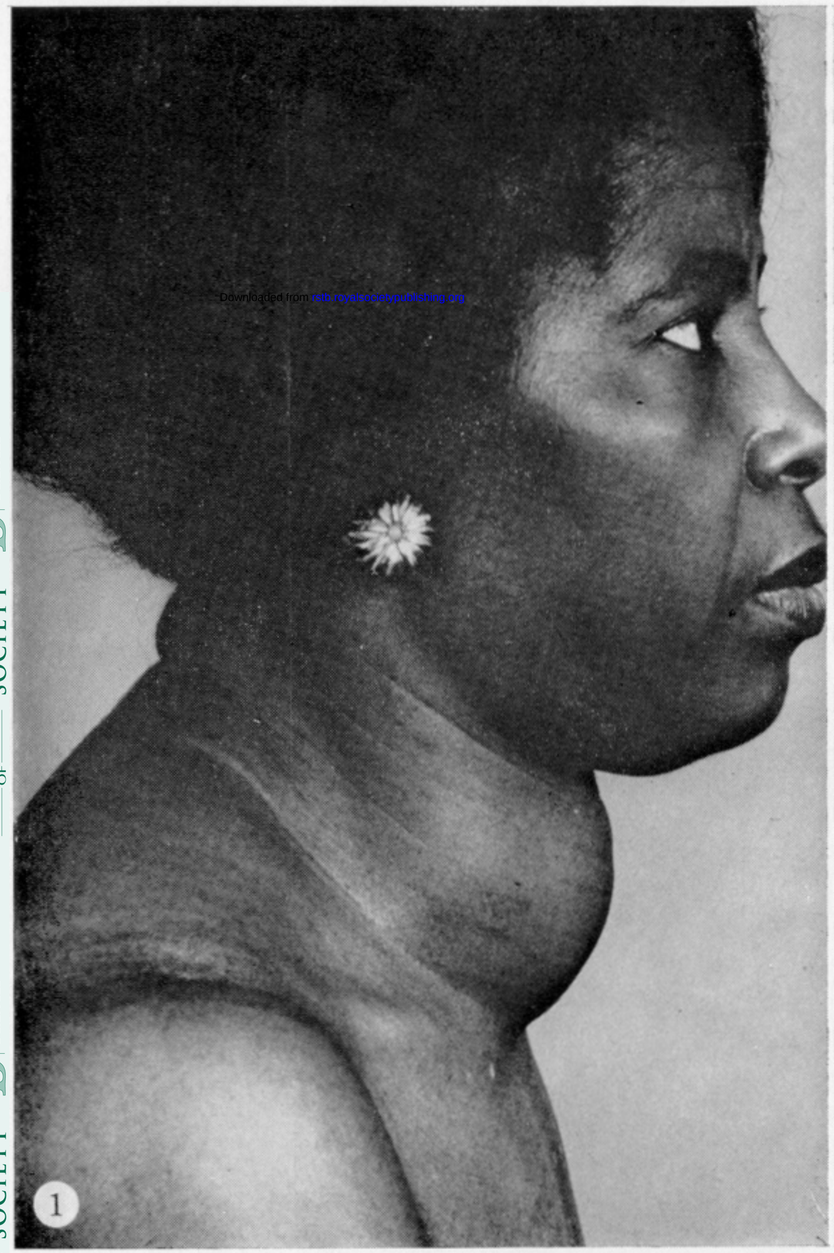
Discussion

M. J. Jackson (*Department of Human Metabolism, University College Hospital, London W.C.1, U.K.*). Dr Moynahan has shown that acrodermatitis enteropathica is a deficiency disorder. A recent publication in the *Journal of Paediatrics* (Garretts, M. & Molokhia, M., **91**, 1977, 492–494.) has described patients with this disease exhibiting normal or elevated levels in body fluids and

tissues. How does Dr Moynahan view the possibility that there are two forms of this disease, only one of which is manifested by Zn deficiency?

E. J. Moynahan. I know of at least four other cases of acrodermatitis enteropathica in which the blood levels of Zn were within the normal range, all of which responded to Zn supplements. Symptomless hyperzincaemia has been described as an inherited trait. It is therefore possible that a similar situation obtains in the patients: perhaps the Zn is more tightly bound to one of the carrier molecules in the blood. We know very little about the transport of trace elements in man, except that oral contraceptives lower the Zn level without untoward effect other than the reduction of the Zn content of sweat and sebum during the luteal phase of the menstrual cycle.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES



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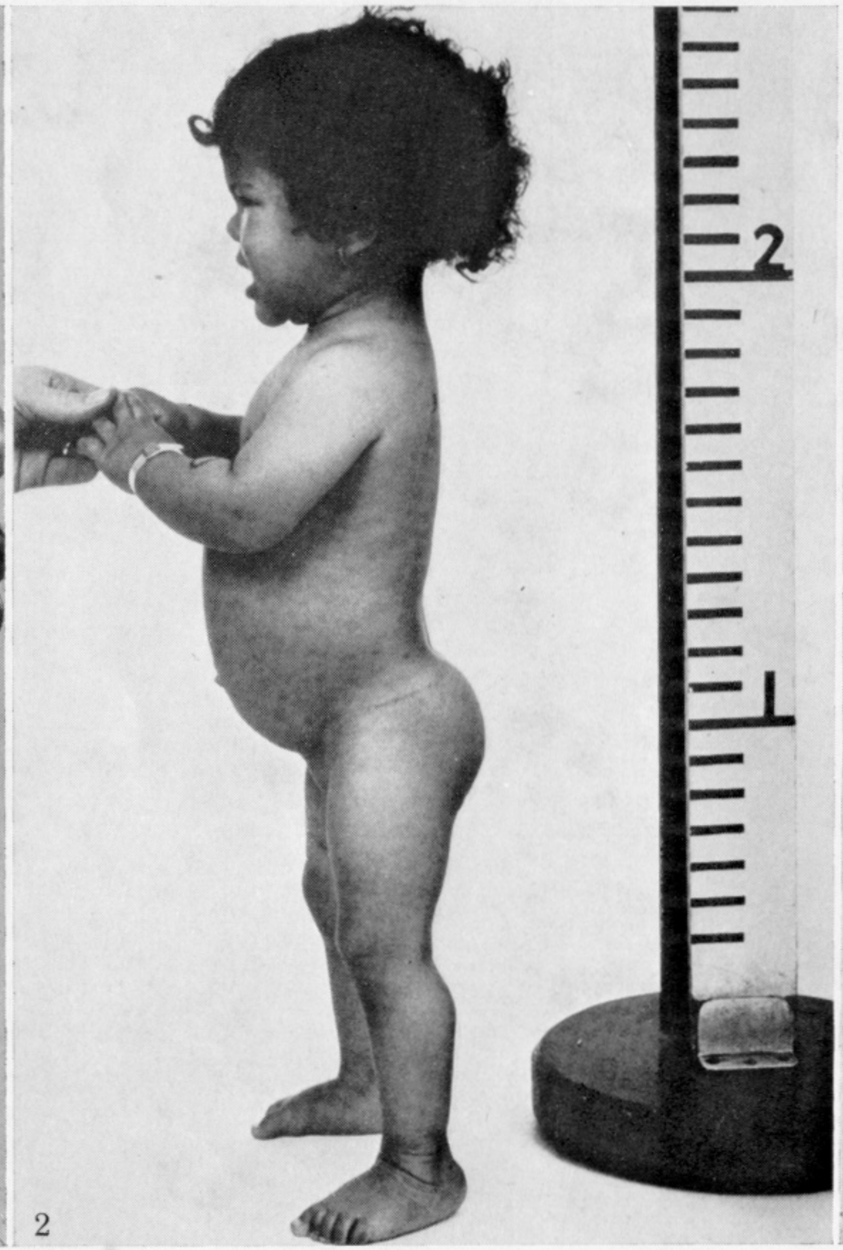

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FIGURE 1. Goitre, typical.

FIGURE 2. Cretin, showing characteristic stance, short stature and delay in walking.

FIGURE 3. Acrodermatitis enteropathica, showing eruption around mouth, nose and ears. Severe zinc depletion will produce identical changes.

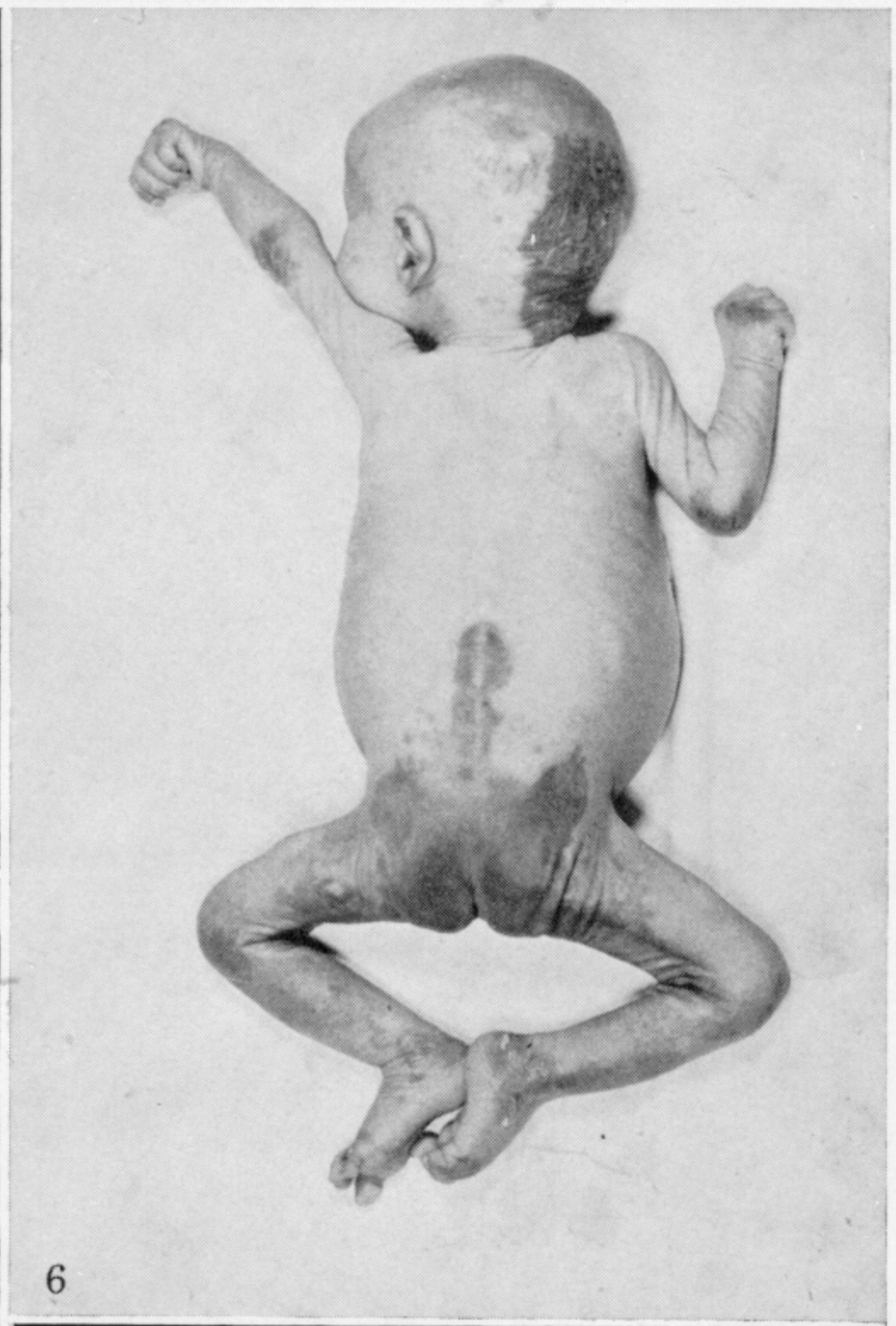

FIGURE 4. Photophobia in acrodermatitis enteropathica; note also paronychia affecting all of the digits from each of which the nail has been shed.

FIGURE 5. Exudative and scaling eruption affecting the external genitalia and buttocks, with blistering and scaling on the knees.

FIGURE 6. Psoriasiform plaques affecting skin over bony prominences; note also total alopecia and paronychiae.

FIGURE 7. Skin changes in Kwashiorkor, with generalized hypopigmentation, scaling and inflammation of skin of abdomen and knees.

FIGURE 8. Genesis of Kwashiorkor: the male twin is better nourished than his sister who is a candidate for Kwashiorkor should she survive to be weaned.