Notes

Trace Elements and Cardiovascular Diseases *

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Studies on trace elements are of particular importance at the present time since man-made alterations of the environment through the use of fertilizers, food additives, food processing and canning and through industrial pollution of air and water may bring about changes in the mineral balance and, as a consequence, in some biological functions. It is well established that several trace elements are of great importance in a number of biological processes, mostly through their action as activators or inhibitors of enzymatic reactions, by competing with other elements and proteins for binding sites, by influencing the permeability of cell membranes, or through other mechanisms. It is therefore reasonable to assume that these minerals would exert an action, either directly or indirectly, also on the cardiac cell, on the blood vessel walls, on the blood-pressure-regulating centres, or on other systems related to cardiovascular function (for instance, by deranging the lipid and carbohydrate metabolism).

The trace-element content of tissues, blood, hair, nails, and excreta of sick and healthy human beings has been studied in relation to a number of diseases (other than nutritional derangements) such as leukaemia, multiple sclerosis, diabetes, azotaemia, hepatolenticular degeneration, schizophrenia (Kanabrocki et al., 1965, 1967), cancer (Kanabrocki et al., 1965, 1967; Samsahl et al., 1965), liver diseases (Kanabrocki et al., 1967; Martin, 1964; Hunt et al., 1963), parkinsonism (Kanabrocki et al., 1967; Mindadse & Tschikowani, 1967), cystic fibrosis [a] and others, including cardiovascular diseases, in an attempt to ascertain the existence of a relationship between disease and abnormal trace-element concentration in the human body. In some instances a direct relationship has been found between changes in tissue mineral content and the severity, duration, or incidence of a disease. Although such changes may be secondary to the degeneration and are not a proof of a real cause–effect relation, yet they might afford clues as to the role played by trace elements in the pathogenesis of a given disease; they might also have a predictive value.

As far as cardiovascular diseases are concerned, there is evidence that trace elements may play a role. A very interesting example is the statistical association found by several investigators in different countries between the softness of drinking-water and the incidence of cardiovascular diseases. Reports from England, Ireland, Japan, Sweden, and the USA show that death rates from ischaemic heart disease and from other cardiovascular diseases are higher in areas served by soft-water supplies than in areas served by hard waters (Kobayashi, 1957; Schroeder, 1960, 1966; Morris et al., 1961; Dingle et al., 1964; Biörck et al., 1965; Mulchay, 1966; Boström & Wester, 1967; Crawford & Crawford, 1967; Crawford et al., 1968).

At necropsy, the prevalence of myocardial scars, of atheroma, and of stenosis of the lumen has also been found to be higher in soft-water areas (Crawford & Crawford, 1967). These findings suggest that the lack of certain minerals in drinking-water is perhaps detrimental to cardiovascular health or, alternatively, that the presence of specific minerals in the water may protect against the disease (Schroeder, 1966).

Other examples are the findings of Schroeder and colleagues that cadmium induces hypertension (Schroeder, 1964, 1965, 1967; Schroeder & Balassa, 1965; Schroeder et al., 1966), and of Wester (1965a, 1965b, 1965c) who detected marked changes in the mineral content of the infarcted heart tissue. Kanabrocki and his colleagues (1964, 1965, 1967) also carried out a series of investigations on the changes in manganese and copper concentrations in the blood and urine of healthy and cardiac subjects. From an epidemiological point of view, valuable information can be gathered from the work of Tipton and her colleagues (1963, 1965) on the tissue mineral content

* Revised version of a paper presented at IAEA Panel Meeting on Activation Analysis in the Study of Mineral Element Metabolism in Man, held in Teheran, Iran, in June 1968.

[a] Bowen, H. J. M., *The use of activation analysis in the study of cystic fibrosis*; paper presented at the IAEA Panel Meeting on Activation Analysis in the Study of Mineral Element Metabolism in Man, held in Teheran, Iran, in June 1968.

in hearts and aortas of healthy subjects as a function of their ethnic origin and geographical distribution. Except for these works, however, no other systematic investigations have been carried out so that our knowledge on the relationship between trace elements and cardiovascular diseases is rather fragmentary. We shall try, nevertheless, to summarize this knowledge.

In this presentation we shall disregard the so-called " bulk " elements, which have been studied extensively and whose physiological actions on the cardiovascular system are fairly well known (for references see Selye, 1958; Bajusz, 1965, 1966), and focus our attention on some trace elements which, on the basis of the available experimental, clinical, and epidemiological evidence, appear to be of interest in cardiovascular diseases and to be worth further investigation.

Cadmium

The trace element that has been studied most extensively in relation to cardiovascular diseases is cadmium, which appears to play a number of detrimental roles, particularly in relation to arterial hypertension. When administered to rats in doses that reproduce the tissue levels of the metal found in North-American subjects, cadmium produces hypertension, hypertrophy of the left ventricle, and sclerosis of the small arteries in kidneys, heart and other organs (Schroeder et al., 1965, 1967; Schroeder & Balassa, 1965; Schroeder, 1964, 1967). It decreases the blood cholesterol level, but, on the other hand, it increases deposition of lipids in the aorta walls and thus it favours formation of atherosclerotic plaques (Schroeder et al., 1965; Schroeder & Balassa, 1965). Cadmium-induced circulatory damage was also reported in testes and placenta of rats (Pařízek, 1964). The hypothesis that cadmium is related to hypertension in man as it is in rats may find support in the clinical observation that this metal is present in high concentration in the kidneys and urine of hypertensive patients (Schroeder, 1965) and, perhaps, also in the results of two epidemiological studies carried out, respectively, by the group of Tipton, Schroeder, and colleagues (Schroeder & Balassa, 1961; Schroeder, 1967; Tipton et al., 1963, 1965) and by Carroll (1966). The first series of studies showed that renal cadmium concentration is practically nil in infants but increases with age, and that it is lower in populations relatively unexposed to industrial civilization and having a low incidence of cardiovascular diseases than in populations from highly industrialized areas such as the USA, where the incidence of cardiovascular diseases is high (Schroeder, 1967; Tipton et al., 1963, 1965).

Carroll (1966), on the other hand, found a positive correlation between the cadmium content in the air and the incidence of hypertension and atherosclerosis in 28 North-American cities. He found no relation with any other air pollutant except zinc, which, as we shall see later on, is always associated with cadmium. Carroll also hypothesized that the higher incidence of cardiovascular disease in coastal areas of the USA might be due to greater consumption of seafood, which is notoriously rich in cadmium. This suggestive hypothesis may find support in another statistical observation, namely, the marked increase in cardiovascular mortality which has occurred in Denmark, Norway, and Sweden over the past several years. More than 10 years ago mortality from cardiovascular diseases in these countries was much lower than in the USA while the consumption of seafood was much higher; this finding was taken as an evidence that seafood, on account of its high content in unsaturated fats, is beneficial to cardiovascular health (Jolliffe, 1959). In recent years, however, heart-disease death rates in these countries increased very sharply although the consumption of seafood remained high. On the basis of this observation, and in agreement with Carroll (1966), one might speculate that increased industrialization brought about greater water pollution by cadmium which, being accumulated by shell-fish and other marine animals, was eventually ingested by man and perhaps contributed to the increase of cardiovascular mortality in these countries.

The experimental, clinical, and statistical evidence so far available indicates that cadmium may be an etiological factor in some types of cardiovascular disease but further investigations are needed to ascertain whether this element really plays a role and to establish what mechanism is involved.

Zinc

Zinc is always associated with cadmium, both in the geosphere and in the biosphere. Carroll (1966) reported that zinc concentration in the air correlates strongly with death rates from hypertension and atherosclerosis, as cadmium does. Schroeder & Buckmann (1967) found that, in rats, the administration of zinc reverses the hypertension induced by cadmium, probably because the two elements compete for the same binding sites, and that a direct relationship exists between blood pressure and molar

ratios of cadmium to zinc in kidneys: when such ratio is higher than 0.35 the animal is likely to develop hypertension. This seems to be true for man also since the renal cadmium-to-zinc ratio increases with age and reaches a peak in the age-group 40–50 years (Schroeder et al., 1967).

As regards the relationship of zinc to atherosclerosis, a few Soviet investigators studied the behaviour of this element in the aorta wall of atherosclerotic subjects. The results, however, were contradictory: some authors reported that zinc concentration in the aorta wall increases in atherosclerosis (Bala & Plotko, 1967; Račinskij, 1967; Sosunov & Malik, 1967) whereas others found that it decreases (Volkov, 1962). Quite recently, the beneficial effect of zinc therapy in atherosclerotic patients has been reported (Herzel, 1968). Zinc appears to be related also to myocardial infarction. The concentration of this mineral decreases in the injured heart tissue (Van Peenen & Patel, 1964; Wester, 1965a, 1965b); this decrease is perhaps related to the disappearance of lactic dehydrogenase, a zinc enzyme, from the infarcted heart tissue. It decreases also in the serum of infarcted patients (Wacker et al., 1956a, 1956b).

Manganese

Manganese also seems to play a role in atherosclerosis: it prevents the development of experimental atherosclerosis in rabbits (Kolesnikov, 1968; Amdur et al., 1946) and has a beneficial effect on lipid metabolism in atherosclerotic patients (Kolesnikov, 1958); the manganese content of the heart and aorta of atherosclerotic subjects is lower, and that of plasma is higher, than in healthy controls (Volkov, 1962; Bala & Plotko, 1967). In myocardial infarction a sharp decrease of manganese content occurs in the injured myocardium (Griffith & Hegde, 1959), followed by a marked increase in plasma and serum (Kanabrocki et al., 1964, 1967; Hegde et al., 1961). This increase is so rapid and specific that it may be used as a diagnostic indicator of a recent myocardial infarction (Hegde et al., 1961). The urine of cardiac patients also shows a higher manganese concentration than that of healthy controls (Kanabrocki et al., 1965).

Chromium

Another trace element that appears to exert a beneficial effect on atherosclerosis is chromium. Experiments in rats show that chromium deficiency is associated with a higher prevalence of aortic plaques whereas a life-time administration of this metal in trace amount prevents the formation of atheromatous lesions, decreases the blood cholesterol level, and prolongs the life-span of the animals (Schroeder & Balassa, 1965; Schroeder & Buckman, 1967; Schroeder, 1967). Contrary to cadmium, whose lowering effect on the blood cholesterol level results in deposition of cholesterol in the aorta walls, chromium facilitates cholesterol catabolism and excretion (Schroeder & Balassa, 1965). Also, the results of epidemiological studies indicate that this element may be related to cardiovascular diseases (Schroeder, 1967; Tipton et al., 1965). It appears that tissue levels of chromium in populations with a high incidence of cardiovascular diseases, such as North Americans, decrease markedly with age, sometimes to almost complete depletion, whereas in populations with a lower incidence of cardiovascular diseases, Africans and Orientals, for instance, these levels remain high. The chromium content in the hearts of these subjects is 4 times as high as in North American subjects; in the kidneys and aortas it is 7 times as high. The depletion of body chromium in North Americans may be due to excessive consumption of refined sugars, typical of prosperous countries, which causes an increase in the urinary excretion of this mineral (Schroeder, 1967). If we also bear in mind that refined sugars contain little chromium whereas raw sugars, which are consumed mostly in less affluent countries, contain appreciable amounts of it (Schroeder, 1967), and that a positive relationship has been detected between the amount of refined sugars consumed and cardiovascular mortality (Yudkin, 1964), then the hypothesis that dietary chromium might play a role in preventing atherosclerosis seems justified. Additional support for this hypothesis may be found in a recent report (*Nutr. Rev.*, 1968) which reveals that chromium prevents glucose intolerance in animals and in man and has beneficial effects on carbohydrate metabolism.

Cobalt

So far as cobalt is concerned, its relationship to atherosclerosis is not yet clear. When injected into rabbits and chickens, it increases both the blood cholesterol level and the incidence of atherosclerosis (Caren & Carbo, 1956; Tennent et al., 1958; Mukherjee et al., 1966), but when it is fed to these animals it reduces the incidence and severity of the atherosclerotic lesions (Tennent et al., 1957, 1958; Griffith & Hegde, 1959). However, when given orally

to man for therapeutic purposes, it may cause hypercholesteraemia. Its mode of action in increasing the blood cholesterol level is debated: according to Caren & Carbo (1956) the increase may be due to the destruction of the pancreatic alpha-cells caused, in rabbits, by injection of cobalt, but Tennent et al. (1958) found no effect on these cells when cobalt was injected into chickens.

In atherosclerotic subjects the cobalt content of the heart and aorta is higher than that of healthy controls (Volkov, 1962; Sosunov & Malik, 1967); in myocardial infarction, instead, the injured heart tissue loses cobalt (Wester, 1965a, 1965b).

At least one type of cardiomyopathy seems to be related to cobalt intake: this is the beer-drinkers' cardiopathy that occurred in Quebec City between August 1965 and April 1966 and was described by Morin & Daniel (1967). This syndrome was characterized by cardiac enlargement and failure and a high mortality rate, and it occurred only in heavy drinkers of beer. It was found that, one month before the syndrome appeared, a Quebec brewery had added a considerable amount of cobalt sulfate to their beer to improve the stability of the foam. Exactly one month after this procedure was discontinued the syndrome disappeared. A similar phenomenon was reported also from Omaha, Nebraska (McDermott et al., 1966; Sullivan et al., 1968), and from Louvain in Belgium (Kesteloot et al., 1966, 1968).

Cobalt alone probably cannot be held responsible for this " beer-heart " syndrome, since it is not very toxic and is rapidly excreted. Besides, even in heavy drinkers of beer the amount of metal ingested was lower than the amount given to patients for therapeutic purposes. It may be, however, that in association with some other factor, such as malnutrition, perhaps, or the effect of the alcoholic vehicle, cobalt might have precipitated the onset of the syndrome. It appears that cobalt has a certain degree of myocardial toxicity: when administered to animals it is deposited in the myocardium (Blanquet et al., 1965) where it exerts a detrimental effect on myocardial function (La March & Est, 1960; Jalavisto et al., 1965) and causes diffuse myocardial degeneration (Heraut, 1962).

Arsenic

A parallel may be drawn between the Quebec cardiomyopathy episode and the " epidemic " of heart failures which occurred among beer-drinkers in Manchester in 1900. The Manchester syndrome, however, was ascribed to beer contamination by arsenic (Reynolds, 1901), or, at least, to enhancement of the toxic effect of arsenic by the alcoholic vehicle (Kelynack, 1901); as reported by Selye (1958) it appears that arsenic may cause myocardial necrosis both in animals and in man.

Vanadium

Vanadium reduces the cholesterol level in plasma and in the aorta in rabbits and in healthy human subjects as well (Mountain et al., 1956; Curran et al., 1959; Lewis, 1959; Schütte, 1964, Korkhov, 1965). Its anti-atherosclerotic action appears to be due to interference with cholesterol synthesis by inhibiting utilization of mevalonic acid (Curran et al., 1959) and also to acceleration of cholesterol catabolism (Mountain et al., 1956). It may be of interest to note that hard waters, whose consumption is statistically associated with a lower incidence of cardiovascular diseases in many areas of the world, contain vanadium whereas soft waters do not.[b] Also Schroeder (1966) found a significant negative correlation between the vanadium content of municipal waters and atherosclerotic-heart death rates.

Nickel

As regards nickel, D'Alonzo & Pell (1963) found that its plasma level increases sharply following myocardial infarction. According to these authors and similarly to what has been envisaged for manganese (Hegde et al., 1961), the rapid increase in the concentration of nickel in the blood may perhaps be used as a diagnostic indicator of recent myocardial infarction.

Silicon

While all the trace elements we have examined so far play a metabolic role in atherosclerosis, by either inhibiting or favouring cholesterol synthesis, catabolism, excretion, or deposition in the artery walls, silicon instead seems to play a functional role since, according to Loeper et al. (1966), it protects the elastic state of the artery walls and maintains the intima impermeable to lipid infiltration. The highest concentration of silicon is found in the aorta, mainly in collagen and elastin. Its content in the aorta walls decreases with age and in atherosclerosis, even if this is still at an early stage, thus suggesting an association between lack of this element and harden-

[b] Strain, W. H., *Effects of some minor elements in animals and people*; paper presented at the meeting of the American Association for the Advancement of Science held in Denver, Colo., USA, on 29 December 1961.

ing of the arteries. Loeper et al. also proved that atherosclerosis experimentally induced in rabbits regresses if the animals are fed silicon salts.

Selenium

Selenium has been reported by several authors to prevent some types of cardiac necroses of nutritional origin in cattle. Selenium deficiency causes cardiac necrosis in mice (Selye, 1958) but not in rats. In dogs, on the other hand, injections of selenium in trace amounts produce cardiac damage and blood-pressure changes. Since the results of animal experiments are contradictory, and pertinent information concerning man is lacking, the role played by this element in cardiocirculatory function is poorly known and further studies will certainly be needed.

Fluorine

Fluorine may exert both a beneficial and a detrimental effect on cardiovascular function. During an epidemiological survey on osteoporosis in the USA, Bernstein et al. (1966) found that the incidence and the severity of aortic calcification were lower in areas supplied with highly fluoridated waters than in non-fluoridated areas. It seems that fluorine interacts with calcium, and favours calcium localization in the bone, thus preventing its accumulation in the walls of the blood vessels. These authors considered that high doses of fluorine might be useful as a preventive measure against calcification of the arteries. In opposition to this apparently beneficial effect, however, it has been proved that large doses of fluorine produce, at least in rats, focal myocardial necroses associated with lesions of the cerebral cortex (for references, see Selye, 1958).

Copper

Kanabrocki et al. (1964, 1965, 1967) observed a slight increase in the copper level in the serum, and a significant increase in the urine, of patients suffering from myocardial infarction. A similar increase in the serum was also found by Adelstein et al. (1956), by Hanson & Biörck (1957) and by Harman (1963). The latter author reported some interesting findings concerning the relation of copper to atherosclerosis and coronary heart disease (Harman, 1963, 1964, 1965, 1966, 1968). Starting from the assumption that oxidation of serum and arterial deposit lipids may be involved in the initiation of atherosclerosis by facilitating conversion of fatty streaks into fibrous plaques, he postulated that copper, a good lipid oxidation catalyst, may play a role in this process and may enhance atherogenesis. Indeed Harman (1964, 1966, 1968) found that in experimental animals the addition of copper to the diet resulted in a higher degree of atherosclerosis and that human subjects with a history of myocardial infarction have a significantly higher serum-copper concentration (Harman, 1963). He also found (1965) that soft drinking-waters, whose use was repeatedly found to be associated with higher cardiovascular mortality rates (see above), have significantly higher concentration of copper than hard waters. As a result of his findings that serum copper levels are positively correlated with coronary heart disease, Harman (1963) postulated that determinations of this metal in serum may aid in identifying coronary-prone individuals and that lowering of copper levels by dieting or chemical means may decrease the probability of development of atherosclerosis.

In atherosclerotic subjects the copper content of the aorta wall decreases (Bala & Plotko, 1967; Račinskij, 1967) while that of the myocardium increases (Račinskij, 1967). It has also been reported that copper deficiency causes defective synthesis of collagen and elastin in the aorta and other blood vessels (Reinhold, 1964), thus damaging the elastic properties of the blood vessel walls.

Discussion

The information we have reviewed above is summarized in Table 1, which shows the trace elements listed according to the allegedly beneficial or harmful effects they seem to have on cardiovascular function; Table 2 shows the changes in tissue mineral concentration occurring in association with atherosclerosis and myocardial infarction.

The cardiovascular diseases—or some of them at any rate—may, like many other diseases, be due to metabolic disturbances caused by mineral imbalance; in turn, they may cause secondary changes in the mineral content of some tissue. Some of these changes can be detected very soon after a myocardial insult; others appear to be very specific and occur not only in the blood or in whole organs but also in different parts of the same organ. Concentration differences have been detected between the injured heart tissue and the non-injured tissue in myocardial infarction; between atria, ventricles, and interventricular septum; between the conductive system and the myocardium; and also between different layers of the aorta walls in atherosclerosis. The available information, however, is still of a pre-

TABLE 1
RELATION OF TRACE ELEMENTS TO CARDIOVASCULAR FUNCTION

Elements	Alleged beneficial effects	Alleged harmful effects
Mn	Protects against atherosclerosis	
Cr	Protects against atherosclerosis	
V	Protects against atherosclerosis	
Co	Protects against atherosclerosis (orally)	Induces atherosclerosis (when injected)
Zn	Protects against hypertension	
F	Protects against calcification of aorta	Produces focal myocardial necrosis (in large doses)
Se	Protects against cardiac necrosis	Damages the heart and produces blood pressure changes
Si	Maintains elasticity of blood vessels	
Cu	Maintains elasticity of blood vessels	Enhances atherogenesis
Cd		Induces hypertension and atherosclerosis
As		Induces focal myocardial necrosis (in large doses)

liminary nature. We do not know whether the changes in tissue mineral concentration that have been detected in the hypertensive, the atherosclerotic, and the cardiac subjects as compared with healthy controls represent a cause or an effect of the disease. Neither do we know, from an epidemiological point of view, whether the differences in tissue mineral concentration existing among various populations having different cardiovascular mortality rates represent a true etiological factor or are simply a statistical association with no cause–effect relationship.

Although we are still far from understanding the relation of trace elements to cardiovascular diseases, it is most likely that such a relation does exist. Many clinical, epidemiological and experimental data point to it. The detection and the interpretation of tissue mineral concentration changes which occur in association with cardiovascular diseases will certainly add to our knowledge of the etiology and pathogenesis of these diseases, may open new avenues to prevention and therapy, and may supply new tools for diagnostic and prognostic evaluations. Very minute concentration changes, even of nanogram amounts, can be detected by the very sensitive modern techniques of neutron activation analysis, atomic absorption spectrophotometry and others. Now that these analytical procedures are available, and are continuously improving, it would be highly expedient that co-ordinated efforts be undertaken by various investigators to explore systematically the problem of trace elements in relation to cardiovascular diseases. Such investigations may offer only fragmentary information in relation to the total

TABLE 2
CHANGES IN TISSUE MINERAL CONTENT IN ATHEROSCLEROTIC AND CARDIAC SUBJECTS AS COMPARED WITH HEALTHY CONTROLS

Increase		Decrease	
Atherosclerosis			
Co:	Heart, aorta		
Fe:	Aorta		
Mo:	Aorta		
Pb:	Aorta, blood		
Ag:	Aorta		
Cu:	Heart	Cu:	Aorta
Zn:	Heart, aorta	Zn:	Plasma
Mn:	Plasma	Mn:	Heart, aorta
		Si:	Aorta
Myocardial infarction			
Ba:	Heart [a]		
Br:	Heart [a]		
Sb:	Heart [a]		
Cu:	Serum, urine		
B:	Serum		
Ni:	Serum		
Mn:	Serum	Mn:	Heart [a]
Mo:	Serum	Mo:	Heart [a]
Ca:	Serum	Al:	Heart [a]
		Rb:	Heart [a]
		Co:	Heart [a]
		Cs:	Heart [a]
		Zn:	Heart,[a] serum
		Fe:	Serum

[a] Injured heart tissue.

mechanism; however, they may also offer information of paramount importance to the control of cardiovascular diseases. Most certainly they would be a worthwhile effort.

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Evolution sérologique de l'infection à *Plasmodium malariae*: variations du titre des anticorps fluorescents après traitement radical *

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L'immunité antipaludéenne — si controversée pendant la première moitié de ce siècle — a acquis une passionnante actualité depuis l'essor pris en cette dernière décennie par les études d'immunologie parasitaire.

L'application avec succès de la réaction d'immunofluorescence pour la mise en évidence des anticorps antipaludéens, tout comme la possibilité de leur détermination quantitative au cours des infections par différentes espèces de plasmodiums, ont ouvert aux recherches immunologiques de larges perspectives non seulement théoriques, mais aussi d'application pratique immédiate. C'est ainsi que les données fournies par la technique des anticorps fluorescents permettent le diagnostic, tant actuel que rétrospectif, du paludisme évolutif ou latent; de même, elles offrent la possibilité d'une évaluation épidémiologique plus efficace concernant la situation du paludisme dans les zones où, grâce aux programmes d'éradication, la maladie est devenue hypo-endémique ou a été « éliminée ».

Davantage encore, certains auteurs préconisent l'application de la réaction d'immunofluorescence pour l'appréciation de l'efficacité des mesures de lutte utilisées dans le cadre des programmes d'éradication. On a même suggéré qu'elle pourrait fournir des précisions au sujet des « médicaments capables

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