Trace Elements in Relation to Cardiovascular Diseases

A WHO/IAEA Joint Research Programme

by Dr. R. Masironi (Cardiovascular Diseases Unit, WHO, Geneva)
and Dr. R.M. Parr (Medical Applications Section, IAEA, Vienna)

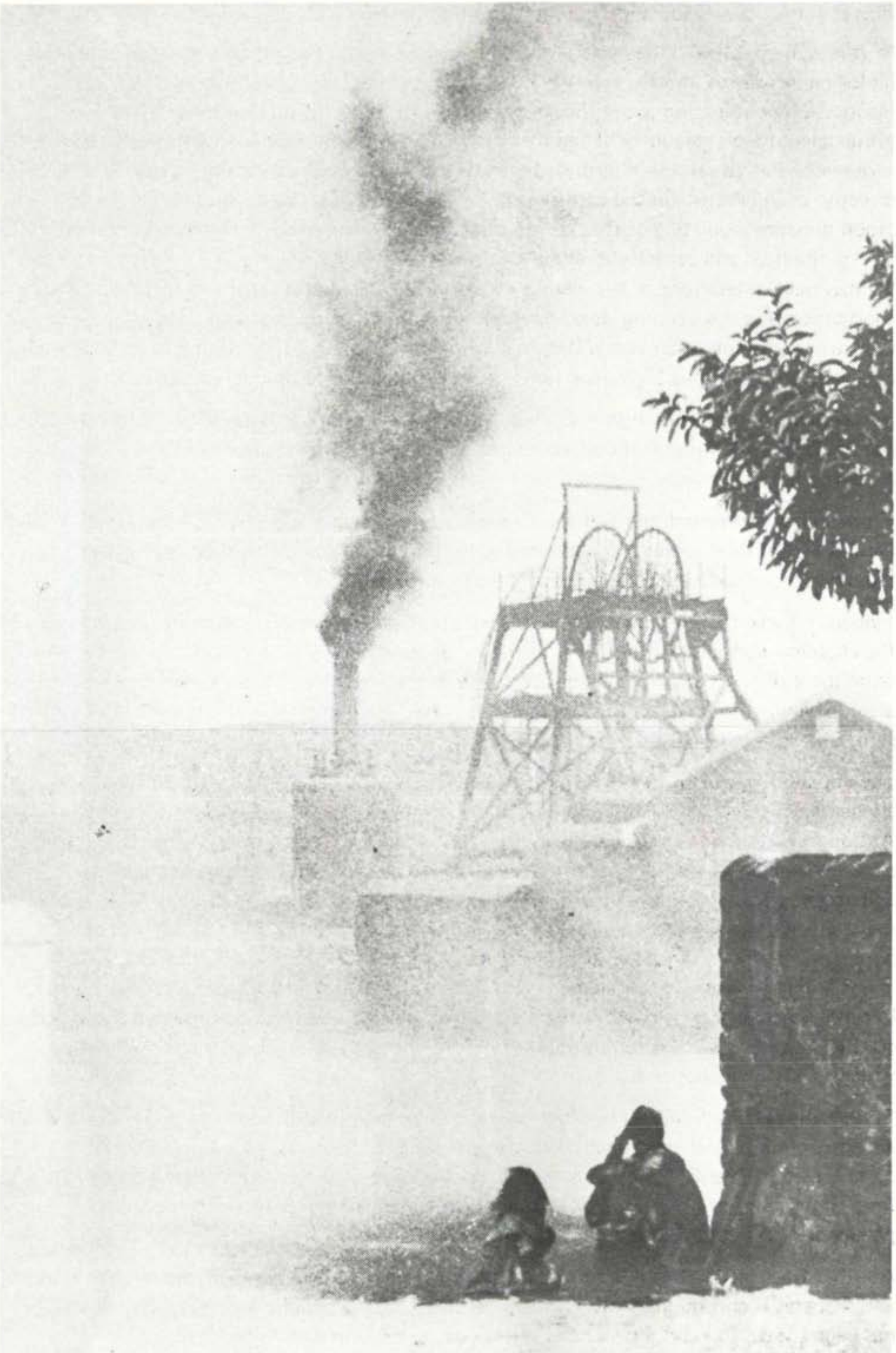
For the past four years the World Health Organization and the International Atomic Energy Agency have been jointly coordinating investigations at an international level on the role possibly played by stable trace elements in the aetiology of cardiovascular diseases, and the use of nuclear techniques in studying these elements.

Cardiovascular diseases (particularly atherosclerosis and ischaemic heart disease) are the major epidemic of modern times in the technologically advanced countries, where they account for roughly 50% of all causes of death. The incidence of these diseases is characterized by two alarming trends. Firstly, it seems to be related to the economic and technological development of a given country or group of countries; among the so-called "primitive" population groups which are relatively unexposed to technological civilization, coronary heart disease is practically non-existent. Secondly, it is constantly increasing, the highest proportional increase being in the younger and more productive strata of the population. In addition, within the same country, there are significant differences in cardiovascular mortality rates according to geographical location.

Geographical and temporal differences in cardiovascular mortality were found to be associated with such factors as consumption of dietary fat, blood cholesterol levels, sedentary life, smoking etc. but a cause-to-effect relationship could not be clearly ascertained.

Other factors which could underlie population differences in susceptibility to cardiovascular diseases should therefore be investigated. One of these other factors, which is related to both the geographical location and to the technological development, is the trace element balance of the environment which, through water and the food chain, may be reflected in the trace element balance of the human organism.

All types of pollution contaminate the environment and alter the natural trace element balance. Research is now trying to establish whether this is reflected in the trace element balance of the human organism, and how this effects susceptibility to cardiovascular diseases. This photo: Dust in a coal-mining area in India – WHO/ILO ▶



This point of view is substantiated by two hypotheses:

- 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 also exert an action, either *directly, or indirectly, on the cardiac cell, on the blood vessel walls, on the* blood-pressure-regulating centres, or on other systems related to cardiovascular function such as, e.g. the lipid and carbohydrate metabolism.
- Man-made alterations of the environment, such as the use of fertilizers, food additives, food processing and canning, treatment and softening of drinking water, and the industrial pollution of air and water, may bring about changes in the mineral balance and, as a consequence, in some biological functions, including the cardiocirculatory function.

In recent years, epidemiological, clinical, pathological and experimental evidence has accumulated which justified undertaking deeper studies of trace elements in cardiovascular diseases.

From an environmental point of view, recent work carried out in the USA has revealed that cardiovascular death rates are associated with the type of soil, since they are higher in areas where the soils are deficient in minerals, and vice versa.

Evidence is also available concerning the relationship between cardiovascular death rates and the chemical composition of drinking water. Several studies have shown that death rates from these diseases are inversely correlated with the hardness of local water supplies; areas served by hard water usually experience lower cardiovascular death rates than the areas served by soft water.

The explanation of this may lie in the presence or absence in the water of certain trace elements which could be either beneficial or harmful to cardiocirculatory function. Although we do not yet possess clear-cut hypotheses as to which trace elements are beneficial and which are harmful, some suggestions may be made on the basis of epidemiological and of experimental studies, which indicate that Cr, Zn, Mn, V, F, Si and Cu may be beneficial to cardiocirculatory function, whereas elements like Cd, for its alleged hypertensive effect, as well as Pb and Co, may be harmful. Most likely, however, it is not a single major or trace element that makes up the so-called "water factor" in cardiovascular diseases, but rather a combination of them. The modern trend in this type of study is that it is the interrelationship of ions and relative ratios of the various elements which must be emphasized.

Besides the geochemical and hydrochemical studies mentioned above, there are also several autopsy, clinical, and experimental studies pointing to a possible relationship between certain trace elements and cardiovascular disease. One of the elements that has been studied most extensively in this respect is cadmium, which appears to play a detrimental role particularly in relation to arterial hypertension.

Another trace element that is being extensively studied in relation to cardiovascular diseases and diabetes is chromium, which instead seems to exert a beneficial effect. This element has been shown to exert a beneficial effect against experimentally-induced atherosclerosis, by preventing the formation of atheromatous lesions and by decreasing the blood cholesterol level. But perhaps the most interesting finding concerning chromium is that this element is essential for maintaining normal glucose tolerance and is a cofactor with insulin. Since diabetes is an important risk factor in the development of atherosclerosis and myocardial infarction, the study of Cr in relation to these diseases is certainly relevant.

In spite of the great amount of work that has been done on the relationships between trace elements and cardiovascular diseases, the evidence is still fragmentary. The nature of the correlations — whether it is a cause-to-effect relationship or simply a statistical association — is still unknown. The mechanisms of action are also poorly understood.

Systematic and internationally coordinated investigations are needed to elucidate these problems, and the World Health Organization, in collaboration with the International Atomic Energy Agency, has therefore started research activities in this field.

SCOPE OF THE JOINT RESEARCH PROGRAMME

The WHO/IAEA research programme on trace elements in relation to cardiovascular diseases is based on two projects dealing with autopsy material. (The two organizations also collaborate, although less extensively, on a number of other projects dealing, e.g. with trace elements in water and food, and in living population studies). The two main projects are:

1. A study of trace elements in human tissues in relation to ischaemic heart disease

The aim of this study is to ascertain whether trace element concentrations in autopsy samples of human tissues are related to ischaemic heart disease as a cause of death, and whether they differ according to the geochemical environment in which the person had lived.

The elements presently considered to be of primary interest in this study are Cd, Cr, Cu, Mo and Zn. The trace elements I, Li, Ni, Pb, Se and V, and the bulk elements Ca, K, Mg and Na are also of interest, but their importance is of secondary priority.

2. A study of cadmium and zinc concentrations in human kidney and their relation to arterial hypertension

The aim of this study is to determine the mean concentrations of cadmium and zinc in human kidney as a function of the geographic and ethnic origin of the subjects and to ascertain whether there is a correlation with mean blood pressure levels or other biological parameters expressive of hypertension. Only Cd and Zn are presently of primary interest.

The samples selected for analysis include heart, liver and kidney for project 1 and kidney only (but separated into cortex and medulla) for project 2. They are chosen as far as possible to exclude gross localized lesions or other evident inhomogeneities and are drawn from different groups of people according to a protocol drawn up for use by the cooperating pathologists. Of primary interest are healthy accident victims and people who have died of ischaemic heart disease.

Since the elements of interest are present in the tissues at concentrations of a few micrograms per gram or even much lower, great care is needed to avoid metallic contamination of the tissue specimens. Handling of the samples is kept to a minimum and plastic or other non-metallic instruments are recommended for this purpose. All types of chemical fixative are avoided; the specimens are preserved instead by freezing and must be shipped to the analytical laboratory in a refrigerated container.

ANALYTICAL METHODOLOGY

The analytical problem posed by this programme is one which tests the limits of present-day analytical technology. Some of the trace elements of interest occur in tissues in concentrations of only a few parts in 10^9 and are therefore extremely difficult to detect. A further complication is the requirement to analyse as many elements as possible in samples which, for practical reasons, are limited in size to a gram or so.

One of the very few analytical techniques available to tackle this problem is that of neutron activation analysis, whereby the sample is irradiated with neutrons in a high-flux nuclear reactor in order to convert some of its constituent atoms into radioactive isotopes. A subsequent measurement of this induced radioactivity, usually made after a suitable radiochemical separation has been carried out, provides a very sensitive and specific analytical method which, in principle, is applicable to 75 of the 81 stable elements. Neutron activation analysis is not the only applicable technique for this purpose, and several of the participants in the present programme are using other methods, such as atomic absorption. The main burden of the analytical work, however, is borne by activation analysis.

A report will soon be available outlining the methods currently in use, which were discussed at a recent research coordination meeting in Vienna. For some of the elements of interest (e.g. zinc) it is possible to make non-destructive analysis (i.e. without the need to dissolve the sample and to apply radiochemistry). For the more difficult elements such as chromium, a radiochemical separation by ion-exchange, solvent extraction or any other appropriate technique is necessary before the radioactivity can be measured. Figure 1 shows an automated solvent extraction system developed under contract for this purpose by the UK Atomic Energy Authority. It is controlled by a conventional magnetic tape recorder and, in its present version, can process two samples simultaneously in about 30 minutes. Following radiochemistry, the samples are subjected to gamma-ray spectometry using either a Na I (Tl) or Ge (Li) detector. The final results of the analysis are calculated by means of a computer program.

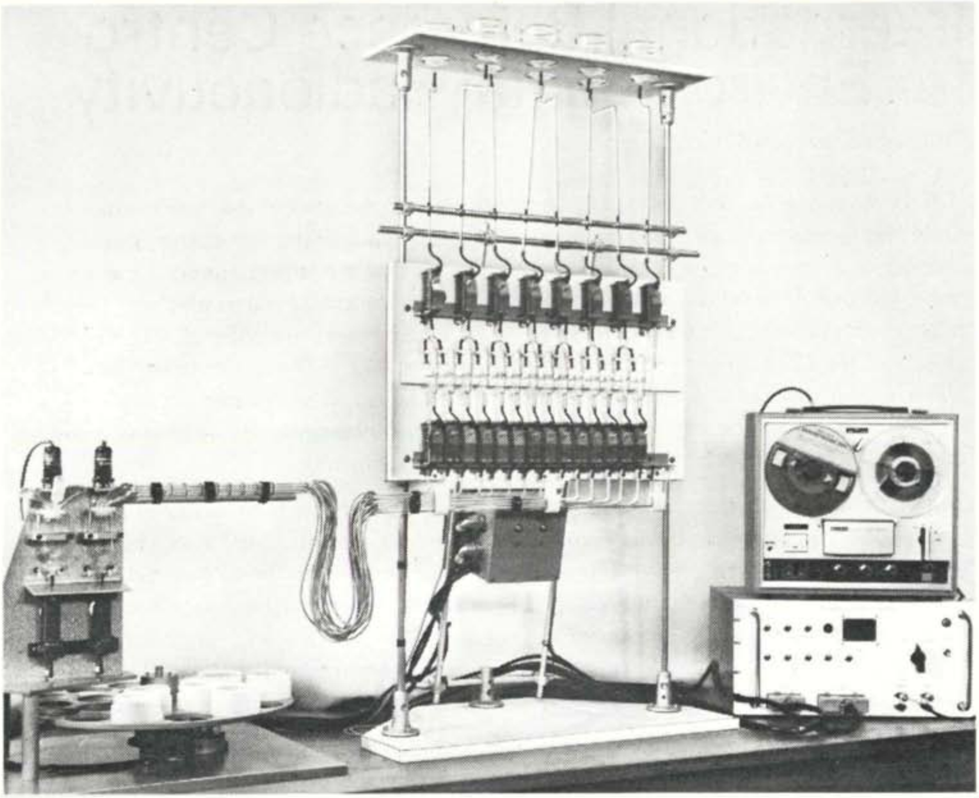
ORGANIZATION OF THE JOINT RESEARCH PROGRAMME

The programme is administered and financed jointly by WHO and IAEA. WHO is mainly responsible for arranging the collection of samples and for assessing the statistical significance of the analytical results reported; IAEA's main role is to arrange for the analyses and to ensure the proper observance of quality control.

Specimens for project 1 have been collected from pathological institutes in Chicago, Manila, Jerusalem, Prague, Stockholm, Sofia and Athens, and for project 2 in Salvador (Brazil), Hong Kong, Singapore, Helsinki, Malmö, Ibadan and Athens. Other collecting centres will join the programme at a later date.

For the analysis of these samples, 12 activation analysis laboratories in 9 Member States are presently cooperating with WHO and IAEA under contract or agreement, as well as the IAEA's own laboratory. Quality control is applied by the distribution of reference materials and duplicate samples prepared, in part, in the IAEA laboratory.

The organization and progress of the programme are under review at periodic coordination and planning meetings. Although one or two of the analytical laboratories have now



Automated radiochemical separator for the determination of cadmium, chromium, copper, molybdenum and zinc by neutron activation analysis. The samples, in a suitably oxidised form, are introduced into the separator in a dilute sulphuric acid medium. The radionuclides of interest are seperated into three chemical fractions suitable for subsequent measurement with a NaI(Tl) or Ge(Li) detector. Two samples are processed concurrently in about 30 minutes – UKEA Aldermaston

been working on the programme for more than three years, most of them joined only in 1972. A report summarizing the results of the programme to date will be available shortly.

CONCLUSION

Cardiovascular diseases are a problem of major concern to everybody in all countries. However, whereas many public health problems are already solved, or will soon be overcome as a result of the progress of biomedical sciences and of rising living standards, for coronary heart disease the outlook is still rather discouraging. A report to the Executive Board of the World Health Organization stated the following: **"Coronary heart disease has reached enormous proportions, striking more and more at younger subjects. It will result in coming years in the greatest epidemic mankind has faced unless we are able to reverse the trend by concentrated research into its cause and prevention".**

The joint research programme is an example of the type of research which, it is hoped, may throw new light on the aetiology of cardiovascular diseases in man.