

# GEOCHEMICAL ENVIRONMENTS, TRACE ELEMENTS, AND CARDIOVASCULAR DISEASES<sup>1</sup>

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*Growing evidence indicates that relationships may exist between cardiovascular diseases, water quality, and geochemical characteristics of rocks and soils in the environment—though the precise factors involved are not known. This article reviews the current status of work in this field and indicates a number of possible areas for future research.*

The role of trace elements in human health is a matter of growing concern to biomedical scientists, since there is evidence of a relationship between the chemical characteristics of the natural environment and the occurrence of various diseases.

There are three reasons for suspecting that the chemical composition of the environment may be involved in the etiology of cardiovascular diseases.<sup>6</sup> The first is based on the observation, reported by several authors in different countries, that an inverse correlation exists between cardiovascular mortality rates and the hardness of drinking water. Second, it has been reported that in some countries the prevalence of cardiovascular and cerebrovascular diseases may be associated with the type of geological substratum. Finally, there are

indications that excesses and deficiencies of certain trace elements in the body may affect the cardiovascular system.

## Cardiovascular Mortality and Water Quality

An inverse statistical association between mortality from cardiovascular diseases and the hardness of drinking water—i. e., the harder the water the lower the death rates—has been detected in several countries, and there are only minor departures from this trend. A list of the studies in which such an association was found is given in Table 1. In some population groups the statistical association was not highly significant for women only (Biörck *et al.*, 1965; Biersteker, 1967) or for men only (Marzot *et al.*, 1968). In another study the association was found to be influenced by the local temperature (Dudley *et al.*, 1969). Cerebrovascular death rates in Japan were associated with acidic water (Kobayashi, 1957) as well as with soft water (Kamiyama *et al.*, 1969). Although various components of drinking water seem to be more closely connected with cardiovascular diseases in some countries than in others, the fact that a certain degree of association appears in so many different countries suggests that a fundamental aspect of cardiovascular health is involved.

Three studies have been made in which a clear association between cardiovascular diseases and water hardness was not found—namely, studies in Colorado (Morton, 1971) and Oklahoma (Lindeman and Assenzo, 1964)

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<sup>6</sup>“Cardiovascular diseases” is a general term that includes various disease entities. However, the term is used in the present context to indicate the main components, mainly ischaemic heart disease (see *International Classification of Diseases, 1965 revision*, subcategories 410-414) and including coronary heart disease, myocardial infarction, atherosclerotic heart disease, and hypertensive disease (see *International Classification of Diseases, 1965 revision*, subcategories 400-404).

TABLE 1—Countries where a negative association between cardiovascular mortality and water quality has been found.

Country	Study	Disease mortality group	Water characteristics and main constituents
Canada	Anderson <i>et al.</i> (1969, 1971)	Coronary disease (sudden deaths only)	Total hardness
Finland	Häsänen (1970)	Diseases of the circulatory system (clinical disability)	Ca, I, Br, Cl; specific conductivity
Finland	Karvonen <i>et al.</i> (unpublished data)	Ischaemic heart	Total dissolved solids; Ca, Mg, V, Mn, Fe, Sr, Zn, Br, Ti, pH
Ireland	Mulcahy (1966)	All cardiovascular disease (low significance)	Total hardness
Italy	Marzot <i>et al.</i> (1968)	Ischaemic heart (males only)	Total hardness; total solids; alkalinity
Italy	Scassellati <i>et al.</i> (1971)	Arteriosclerotic degeneration of the myocardium	Total permanent and temporary hardness
Japan	Kobayashi (1957)	Cerebrovascular disease	Alkalinity CO <sub>3</sub> /SO <sub>4</sub> ratio
Japan	Kamiyama <i>et al.</i> (1969)	Cerebrovascular disease	Total hardness
Netherlands	Biersteker (1967)	Coronary disease (females only)	Total hardness and calcium
Sweden	Biörck <i>et al.</i> (1965)	"Other" degenerative heart and cerebrovascular diseases (females only)	Total hardness and calcium
United Kingdom	Morris <i>et al.</i> (1961) Crawford <i>et al.</i> (1968) Crawford <i>et al.</i> (1971)	All cardiovascular, cerebrovascular, coronary, and "other" heart diseases	Total and temporary hardness; calcium
United Kingdom	Hart (1970)	Coronary heart disease	Total hardness
United Kingdom	Robertson (1968)	All cardiovascular disease	Calcium; total hardness
USA	Schroeder (1960)	All cardiovascular, cerebrovascular, coronary, and hypertensive heart disease	Total hardness; calcium and magnesium
USA	Muss (1962)	All cardiovascular disease in New York City	Total hardness
USA	Schroeder (1966)	Coronary, cerebrovascular, and hypertensive heart disease	Total hardness; specific conductance, dissolved solids; K, Mg, Si, HCO <sub>3</sub> , Cl, Na, SO <sub>4</sub> , Ca, V, Ba, Sr, Li, beta-radioactivity
USA	Dudley <i>et al.</i> (1969)	Coronary heart disease (in warm and temperate areas only)	Total hardness
USA	Peterson <i>et al.</i> (1970)	Coronary disease, hypertension (sudden deaths only)	Total hardness
USA	Masironi (1970)	All cardiovascular disease and hypertensive heart disease	Total hardness; alpha-radioactivity; Cr, V, Zn, Mn, Fe
USA	Sauer <i>et al.</i> (1971)	Cardiovascular disease (renal, coronary)	Total hardness; total dissolved solids; Ca, Mg, Na, K
USA	Groover <i>et al.</i> (1972)	Cardiovascular disease (renal)	Total hardness

within the United States of America, and in a province of Sardinia (Angelillo *et al.*, 1964). On the whole, however, the trend seems clear enough: areas supplied with hard water usually show lower cardiovascular mortality rates than do areas supplied with soft water.

There are suggestions that the higher risk may not involve exposure to soft water for a lifetime or even for many years. Favorable changes in cardiovascular mortality rates were found in areas where the water had been hardened, and unfavorable changes in areas where the water had been softened. These variations in mortality occurred only a few

years after the changes in water hardness had been made (Robertson, 1968; Crawford *et al.*, 1971; Groover *et al.*, 1972).

When an environmental factor appears to affect mortality, it is important to establish whether correlations indicate a direct causal relationship or merely reflect other conditions to which both mortality and the suspected factor are related. In the United Kingdom studies a comprehensive search was made for social or environmental factors that might correlate with water hardness or calcium, but none were found. Rainfall was the only closely associated variable; but this would be expected,

since the high-rainfall areas are mostly the soft-water areas. Given this situation, the possibility of a direct cause-and-effect relationship could therefore be considered.

#### *Pathogenesis*

Theoretically, the association between water hardness and cardiovascular diseases could be linked with any of the pathological processes known to be involved in cardiovascular disease (e.g., mural atheroma, intravascular thrombosis, and hypertension) or with a nonspecific mechanism in cardiac failure. Crawford and Crawford (1967) compared the prevalence of coronary and myocardial disease in soft-water and hard-water areas, and their results pointed to a factor affecting the myocardium; in other words, there was an increased susceptibility of the myocardium in the soft-water area.

Attention was again drawn to the myocardium by the findings of Anderson *et al.* (1969, 1971) and Peterson *et al.* (1970) indicating that the higher death rate from ischaemic heart disease in the soft-water areas of Ontario, Canada, and in the State of Washington, USA, was due entirely to an excess of "sudden deaths." Although Neri *et al.* (1971) could not confirm these findings, the question remains whether deaths due to ventricular fibrillation or some disturbance of myocardial electrophysiology are indeed more common in soft-water areas.

Points emerging from all these studies are that (1) all the main components of cardiovascular mortality may be involved, a point also brought out by the larger national studies (Schroeder, 1960, 1966; Morris *et al.*, 1961; Crawford *et al.*, 1968); (2) ischaemic heart disease, although the largest fraction of all cardiovascular mortality, is neither the most closely nor the most consistently associated with water hardness; (3) hypertension is possibly a common factor. Masironi (1970), using data from 42 states and many counties and communities in the USA, found consistently significant inverse correlations between water hardness and deaths from hypertensive heart disease.

#### *Components of Drinking Water and Their Effect on Cardiovascular Disease*

Several mechanisms could be invoked to explain the apparent relationship of cardiovascular diseases to water quality; for example, hard water could be protective on account of the calcium content, or trace elements could be involved, or soft water could carry toxic elements derived from the soil or distribution pipes.

Calcium, magnesium, and sodium are the principal cations in drinking water, and of these calcium is the one most closely associated with mortality in several studies. Water calcium could be important in two ways. First, it might inhibit the absorption of harmful elements from soil and distribution pipes. Therefore, it may be more important to examine the concentrations of trace elements relative to that of calcium, rather than to measure the absolute amounts present. Second, calcium ions in drinking water might constitute an effective addition to dietary calcium. Although there is disagreement about the contribution that water calcium makes to the total calcium intake, it has been shown in the United Kingdom that hard drinking water may provide a significant amount of this mineral (Widdowson, 1944; Widdowson and McCance, 1943; Murray and Wilson, 1945; Hollingsworth, 1956).

Longer QT intervals in the ECG, which indicate greater susceptibility to dysrhythmias and risk of sudden death (James, 1969), are associated with a low serum calcium concentration (Boen *et al.*, 1962). Since low serum calcium levels were found in soft-water areas (Bierenbaum *et al.*, 1969; Kamiyama *et al.*, 1969), it is possible that the mechanism mentioned above may account for the allegedly harmful effects of soft water on cardiac function. A low intake of magnesium may also contribute to the higher death rates from cardiovascular disease in soft-water areas (Berberian, 1962; Goldsmith and Goldsmith, 1966).

Calcium and magnesium are vitally involved in enzyme systems in the myocardium and in maintaining the electrolyte balance, and de-

rangement of intramyocardial electrolyte exchange may play a crucial role in the pathogenesis of the many syndromes involved in degenerative heart disease (Raab, 1969). An overall balance in intake between calcium and magnesium on the one hand, and sodium on the other, may also be important to the stability of electrolyte balance. In most healthy people dietary minerals will counterbalance environmental variations; but in certain conditions—such as cardiac failure, hypertension, and “stress” with excess secretion of catecholamine in which readjustment to a normal electrolyte balance could be delayed—water lacking calcium and magnesium (and thus favoring retention of sodium) could be harmful. Several studies seem to support the hypothesis that a low calcium intake and a high sodium intake have a detrimental effect on cardiocirculatory function (Elliott and Alexander, 1961; Fatula, 1967; Schroeder *et al.*, 1967; Langford *et al.*, 1969; Kamiyama *et al.*, 1969; Douglas *et al.*, 1969).

There is a considerable volume of literature on the effects of trace elements on processes known to be involved in cardiovascular disease; this has been reviewed by Masironi (1969). It is thought that some elements—e.g., chromium, manganese, and zinc—may have a “protective” effect, mainly as a result of favorably influencing lipid and carbohydrate metabolism. It has also been suggested that a high content of fluorine (Leone *et al.*, 1960), vanadium (Strain, 1961), lithium (Voors, 1970a, 1970b,) or iodine (Häsänen, 1970) in water may be the beneficial factor associated with lower cardiovascular death rates in certain areas. Other elements, such as lead and cadmium, which may be removed from distribution pipes by soft water, are thought to be harmful. In the United Kingdom it was found that the lead content of water that had remained in pipes overnight or for a longer period was high, particularly in some towns supplied with soft water (Crawford and Morris, 1967); this may be relevant when it is considered that higher concentrations of lead were found in the blood and the aortas of atherosclerotic patients than in those of persons

free of the disease (Bala and Plotko, 1967). Schroeder (1969) speculated that cadmium dissolved from galvanized iron pipes could be the cause of hypertension and might be the “water factor.” Several studies have been carried out on the hypertensive effects of cadmium.<sup>7</sup> The suspected effect of soft water in relation to cardiovascular disease could therefore be explained by the absence of certain “protective” elements extracted from distribution pipes. Unfortunately, studies comparing concentrations of trace elements in soft and hard water (Schroeder, 1966; Masironi, 1970; Boström and Wester, 1967; Crawford and Morris 1967; Crawford *et al.*, 1968) have not produced consistent results.

It seems unlikely that the presence or absence of any one element could explain the various findings in different areas. Most of the published work on the subject is concerned with the observation that mortality from cardiovascular and coronary heart disease appears to be related to the quality of drinking water, the most commonly used criteria being hardness and softness; more data on trace elements in drinking water should be collected in order to determine if a pattern occurs.

#### *Cardiovascular Mortality and the Geochemical Environment*

Relationships have been found between cardiovascular diseases and the composition of both drinking water and raw water (Kobayashi, 1957; Häsänen, 1970; Masironi, 1970; Sauer *et al.*, 1971). This indicates that a broader factor, i.e., the geochemical environment, may be involved. This hypothesis finds support also in some geochemical investigations specifically concerned with cerebrovascular (Takahashi, 1967) and cardiovascular (Sauer *et al.*, 1966; Shacklette *et al.*, 1970) diseases. In Georgia and North Carolina cardiovascular disease death rates are closely associated with types of soil,

<sup>7</sup>A list of references is given in “Report of a Meeting of Investigators on Trace Elements in Relation to Cardiovascular Diseases”; Geneva, unpublished document WHO/CVD/71.2.

which differ greatly in their content of trace elements. It has been postulated (Sauer *et al.*, 1966) that trace elements in some of the soils may be either beneficial or harmful to cardiovascular function; this could explain the relationship between cardiovascular mortality rates and the geological structure of the area.

The two areas of contrasting cardiovascular mortality rates in Georgia differ markedly in their geological and geochemical character. An area of low mortality is found in northern Georgia where the substrata consist largely of igneous and metamorphic rocks of Precambrian age (i.e., rocks formed more than about 600 million years ago). They mostly contain crystalline silicate minerals that are only slightly soluble in water at surface temperatures, and it is expected that both ground and surface water in this part of the state will prove relatively poor in trace elements. The soils, however, are comparatively rich in trace elements. Another area, in the central part of Georgia where cardiovascular mortality rates are high, overlies younger rocks of Tertiary age (i.e., rocks about 1-60 million years old) that consist largely of unconsolidated sand, silt, and clay. Trace elements adsorbed on the clay particles and on colloidal materials are easily dissolved by ground and surface waters, and it is expected that the water in this area will prove relatively rich in trace elements. The relative abundance of trace elements in water in these two areas of contrasting cardiovascular mortality rates may be the reverse of that in the soil; soils in the northern area contain larger amounts of trace elements, but the way in which the elements are held may make them less prone to dissolve in water.

On the other hand, preliminary data (Masironi, 1971) suggest that cardiovascular death rates may be higher in some areas overlying old rocks, particularly of Precambrian age. In Europe, for example, Precambrian rocks underlie northern countries—including Scotland, Sweden, Finland, and Denmark, which all have notoriously high death rates from cardiovascular diseases—while countries of the Mediterranean region with underlying geological

formations of the Mesozoic and Cenozoic eras (i.e., formations less than about 200 million years old) have characteristically low death rates. Great Britain is an interesting example, with lower cardiovascular death rates in the southern, geologically younger, part of the country than in the northern, geologically older, part. Norway, with younger underlying rocks than either Sweden or Finland, has a lower death rate from ischaemic heart disease than those two countries.

Precambrian terrains are often characterized by a low availability of trace elements and by relatively soft water. Another feature of the major areas of the world with underlying Precambrian rocks is that, in general, they are covered by podzol or podzolic<sup>8</sup> soils, the upper layers of which have been leached. These observations are consistent with the pattern of association between higher cardiovascular death rates and a general deficiency of most trace elements.

It is interesting to note that podzol and organic soils are characteristically predominant in northern parts of Great Britain and in northeastern Finland, where death rates from coronary heart disease are perhaps the highest in Europe. On the other hand, death rates for cardiovascular disease are very low in countries such as Greece, Italy, Portugal, Spain, and Yugoslavia that have predominantly red and brown Mediterranean soils. Unlike the podzols, which in the northern latitudes originate largely from relatively insoluble granites and gneisses, Mediterranean soils are formed mainly from the more soluble calcareous rocks and plants. Water may extract larger amounts of minerals from these latter soils.

It seems, however, that relatively high cardiovascular mortality rates can also be found in areas that are situated on very young

<sup>8</sup>Podzol soils occur in humid northern regions, especially in areas covered with pine forest; they are characterized by an ash-like stratum in their upper layer. Podzolic soils occur in hardwood forests of humid temperature regions and exhibit a less pronounced ash-like stratum than the podzols; they are commonly subdivided into grey, brown, grey-brown, or red-yellow soils.

formations, i.e. Quaternary deposits less than 1 million years old (Masironi, 1971). Countries (e.g., Hungary and Romania) that lie predominantly on these young formations have higher cardiovascular death rates than neighboring countries (e.g., Poland, western Yugoslavia, and Bulgaria) that have no Quaternary deposits or very few. Belgium is another country situated on Quaternary sediments, and the cardiovascular death rates there are higher than in the Netherlands.

In the Netherlands itself, the highest cardiovascular death rates are found in the south-western region, which overlies the same Quaternary deposits as those in Belgium. Extensive Quaternary deposits occur in the eastern part of Yugoslavia and in the Piedmont and Po Valley of Italy; these regions have the highest death rates from cardiovascular disease in the respective countries. Similar trends can also be detected in the USA; some Louisiana and Arkansas counties in the Mississippi Valley and parts of eastern Florida overlying Quaternary deposits have higher cardiovascular mortality rates than other counties in the same states that are not situated on these deposits. Many of the Quaternary deposits were depleted of trace elements during the extensive weathering and sedimentation processes which produced them.

#### **Chemical Composition of Natural Water in Relation to Rocks and Soil**

The epidemiologic relationships between death rates from cardiovascular diseases, water quality, and the geochemical environment, may be attributed to the fact that the chemical composition of water depends to a great extent on the chemical composition of the geological substrata.

Natural sources of domestic and industrial water supplies are either surface water derived from streams, rivers, ponds, and lakes, or groundwater derived from wells and springs. Most water from wells and springs is called "meteoric," i.e., it has entered the local aquifer (source of groundwater) from the surface after precipitation from the atmosphere. Some water

from wells and springs, however, may be "connate," i.e., water trapped in sedimentary rocks at the time the rocks were formed. The latter is frequently saline.

The further classification of natural water is usually based on its chemical characteristics, particularly on the most common cations and anions present. The most common cations are those of the alkali metals sodium and potassium, and the alkaline earth elements calcium and magnesium. The most common anions are carbonate, hydrogen carbonate, chloride, sulfate, and nitrate. Thus, water is commonly referred to as sodium hydrogen carbonate water or calcium sulfate water, etc., depending on its principal ions. Various mathematical and graphic schemes have been devised for classifying the chemical characteristics of water more rigorously.

The chemical characteristics of ground and surface water are related in a complex manner to the chemical characteristics of the rocks and soils with which it has come into contact, either on the surface or underground. The relationships are complicated by the fact that most water has been in contact with more than one type of rock or soil.

The following processes are believed (Hem, 1959) to be important in determining the chemical characteristics of water: chemical solution and precipitation of molecules and ions on mineral surfaces; ion-exchange reactions; the chemical reduction of sulfate ions by the activity of bacteria; salt-water encroachment in coastal regions; life processes of plants and animals, including the production of carbon dioxide and the accumulation of nitrogen; and human activities such as irrigation and water disposal.

The gross chemical properties of water can usually be inferred from a knowledge of the geological structure of the terrain, and it is often possible, without any chemical analysis, to predict whether the water will be hard or soft. For example, water from limestone terrain tends to be hard, i.e., rich in calcium, magnesium, and hydrogen carbonate ions, because of the composition of the rock and the solu-

bilities of the minerals that form limestone. Water from granitic terrain, on the other hand, tends to be soft, mainly as a result of sodium-rich minerals present in granitic rocks. Water that has come into contact with certain clay minerals tends to be soft (i.e., rich in sodium ions relative to calcium and magnesium ions) on account of ion-exchange reactions.

Sedimentary rocks have a more varied composition than igneous rocks, and this is reflected in the more variable characteristics of water associated with sedimentary rock. Conglomerates and many sandstones are water-bearing because of their high porosity; in many areas they are good sources of groundwater. These aquifers often lack cementing material between the particles or fragments, and they therefore yield water of high purity (i.e., water that is poor in total dissolved solids). Silts, and especially shales, are less pervious to water and rarely form extensive aquifers, but the water derived from shale has a characteristically high level of total dissolved solids. The quality of groundwater derived from limestone and dolomite aquifers varies considerably, depending on their mineral composition and the depth from which the water is taken. This type of water typically contains calcium-magnesium, carbonate, and hydrogen carbonate ions. The magnesium comes mostly from the mineral dolomite, which is a major component of the rock type bearing its name. Varying proportions of dolomite also occur in limestone rock.

Atmospheric water charged with carbon dioxide, that percolates into siliceous rocks, preferentially attacks the alkali minerals. The characteristic ions are then sodium and potassium, carbonate, and hydrogen carbonate. Where the rocks are richer in ferromagnesium minerals, the water typically contains calcium and magnesium, rather than sodium and potassium. Water derived from these rocks also tends to be rich in silicon dioxide.

Although some generalizations can be made about the main chemical constituents of water, far less is known about the trace elements, which are believed to be important for human and animal health. Further studies are needed,

and special attention should be paid to the fact that the trace element composition of raw water may change drastically when the water is treated for human consumption.

### **Some Approaches to Geochemically Oriented Studies of Cardiovascular Epidemiology**

The chemical nature of the environment depends on both natural and artificial factors. In their migration from the rocks—the primary source—the elements follow complex and often reversible paths through soil, ground and surface water, and plant and animal food chains to man. Thus the chemical characteristics of the general environment are controlled by complex interactions involving the various elements. Superimposed on this natural pattern are the effects of human activity: mining, the use of fertilizers and pesticides, water treatment, food processing, etc., which are now usually grouped under the general term “pollution.” These activities alter the natural migration and distribution of elements. As a result of such complicating factors, and because of limitations in mortality and morbidity data, correlations between geochemistry and cardiovascular disease are unlikely to be revealed by cursory investigations. Nevertheless, some consideration of the general geological and geochemical characteristics of epidemiologically contrasting areas may provide some indications for further study. Likewise, observations on the epidemiologic characteristics of areas that differ in their geology and geochemistry may also yield useful information for medical research.

Some suggestions for geochemically oriented studies of cardiovascular epidemiology are as follows: (1) areas overlying rocks of contrasting geological characteristics should be investigated with respect to their cardiovascular disease rates; (2) areas with leached soil and those with relatively unleached soil should be compared; (3) mining and other industrial activities that expose the population to higher than normal amounts of certain trace elements should be studied to determine the health implications of ore deposits and the release of various elements

into the environment during mining and smelting operations.

The population characteristics of areas to be studied should first be examined in order to obtain statistically and epidemiologically significant data. Areas with a dense population are probably unsuitable for study because food and water supplies are generally brought in from a distance. This would upset an evaluation of the relationship between mineral balance in the body and that in the local environment. On the other hand, small, sparsely populated areas will not provide statistically stable health data because the sample size will be too small. Thus the only alternative is to select large, sparsely populated areas which will provide adequate, stable epidemiologic data. In areas with a relatively low population density the people (farmers, etc.) generally have a close relationship to the land, and they tend to consume food that is produced locally and water from wells or springs.

#### *Epidemiologic Studies in Geologically Contrasting Areas*

The first source of data for environmental geochemistry is a good geological map showing the distribution and configuration of geological structures. Other important sources of information are analyses of various types of rock and tables of geochemical data that are available for many regions of possible epidemiologic interest. Although there is no entirely satisfactory substitute for geochemical investigations made on the spot to measure the actual amounts of various elements in the rock, soil, water, plants, and animals, a general knowledge of the local geology is sufficient for predicting, up to a point, the general abundance of elements in the area. When igneous rocks are considered, for example, most of the elements of interest in a study of cardiovascular disease (particularly the allegedly "beneficial" ones—namely, calcium, chromium, copper, magnesium, manganese, vanadium, and zinc) are less concentrated in common granites than in basalts. With regard to sedimentary rocks, all the elements mentioned

above except calcium are less concentrated in sandstones than in shales; and all except calcium, magnesium and manganese are less concentrated in limestones and dolomites than in shales.

It may be expected that further research will narrow the list of elements involved in cardiovascular disease to a few of particular importance or even to a single one. In this event, geological studies could be restricted to particular types of rock differing widely in chemical composition. Meanwhile, investigations of cardiovascular epidemiology's relation to geochemistry will probably continue to implicate different elements or groups of elements in either beneficial or harmful effects on the cardiovascular function.

A useful approach might be to compare cardiovascular disease in areas overlying basaltic and granitic rocks. This would have the advantage that the trace elements would be present in roughly the same type of silicate mineral in each area, and should therefore be released in direct proportion to their abundance under similar conditions of climate and vegetation. It may, however, be difficult to find areas that are large enough to provide stable epidemiologic data. Comparisons of areas overlying shale with areas overlying sandstone may be made more easily since large areas are known that lie mainly over one type of rock or the other. Two difficulties are that both types of rock often occur together and surface water in shale areas is largely derived from subsurface sandstone.

Areas overlying rocks of very different geological age may be suggested for study, for example the extensive Precambrian terrains with sedimentary basins and continental margins covered by Tertiary deposits. Ground and surface waters from Precambrian terrain (which is largely granitic in character) tend to be soft, relatively rich in silica, and generally poor in total dissolved solids. Water arising from Tertiary deposits is likely to be as variable with regard to trace elements as the rocks from which the deposits are formed; it is often hard and rich in total dissolved solids. If the inverse



correlation between water hardness and cardiovascular death rates is proved, these differences in the characteristics of drinking water may account in part for the preliminary observations of Masironi (1971) on death rates from cardiovascular diseases and the age of the rocks underlying the area.

Although a difference in the geological age of the underlying rock by no means reflects any inevitable difference in the abundance and availability of trace elements, the correlation of epidemiologic data with the age of the rock in various study areas could be a first step in extending this kind of investigation on a world-wide scale.

Another useful approach might be to compile health data for areas as small as individual farms, which are commonly located within (and draw their water supplies from) a single geological unit. This approach is being followed by the Environmental Surveillance Center at the University of Missouri, USA. Another approach, adopted by the US Geological Survey in cooperation with the Environmental Health Center of the University of Missouri, is to study pairs of adjacent or nearly adjacent counties throughout the USA that show highly contrasting adjusted cardiovascular-renal death rates. Attempts are being made to identify consistent geological or other environmental features in those counties with either very high or very low rates.

#### *Investigation of Areas with Leached and Relatively Unleached Soil*

Two factors are of major importance in determining the trace element content of the soil. One is the type of parent material from which the soil is formed; the other is the quantity of soluble matter removed by leaching during the development of the soil profile. The parent materials may be of primary importance in azonal soils, i.e., those lacking a well-developed profile; but where the soil profile is well-developed, leaching may produce soils that differ from the parent materials in chemical and mineral composition.

A generalized soil map of the world has been published in the *Yearbook of Agriculture* (1957). Five soil types shown in this map rank in the following order with respect to their increasing tendency to be depleted of trace elements originally present in parent materials: desertic (arid), tundra, chernozemic,<sup>9</sup> podzolic and latosolic<sup>10</sup> soils. A sixth type, mountain soil, varies considerably in the extent of leaching, depending on both the climate and the vegetation.

The desertic soils tend to be less leached on account of the absence of moisture for long periods; tundra soils are also relatively unleached because they are frozen for much of the year. Chernozemic soils are usually well-drained, and leaching occurs frequently. Podzolic soils form under acid conditions in cold regions, where organic matter decomposes slowly; such soils characteristically have highly leached zones in their upper layers. The latosols develop in tropical areas where organic matter decomposes rapidly, but where the water tables are high; they are extensively leached.

The total amounts of trace elements linked with cardiovascular diseases that occur in each of the five main types of soil will depend on many factors, but it is to be expected that the amounts present in water-soluble form will be approximately related to the degree of leaching. The collection of epidemiologic data from various parts of the world according to the main soil types may therefore be of interest.

#### *Investigation of Mining and Associated Industries*

The greatest natural concentrations of many chemical elements in the earth's crust occur in

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<sup>9</sup>Chernozemic soils commonly develop on grass-covered prairies. They are characterized by a thick upper layer formed mainly from decomposed grass and silt and rich in organic matter; these may be the soils most suitable for agricultural use.

<sup>10</sup>Latosolic soils occur mainly in tropical and subtropical regions, and are characteristically reddish in color as a result of the accumulation of iron oxide.

ore deposits that are widely distributed in most parts of the world. Most of the geochemical contrasts in soils and rocks that have already been discussed are small compared with those between the common types of rock and metal ores. According to Hawkes and Webb (1962), zinc is present in ore deposits in concentrations of 80,000 ppm (8 per cent) or more, which represents an enrichment factor of 1,000 times compared with the usual concentration of zinc in common rocks. Enrichment factors of some other elements are chromium, 125; cobalt, 250; copper, 140; manganese, 250; nickel, 95; and vanadium, 300. Many of the elements of interest regarding cardiovascular diseases also occur as minor constituents of ores of other metals; but they are nevertheless present there in much greater quantity than in the common rocks, and they can often be identified by macroscopic examination.

The occurrence of an ore deposit can and often does have a profound effect on the natural geochemistry of the area, but the influence of such deposits is many times greater when the ores are mined and their metal extracted. The epidemiologic characteristics of areas surrounding ore-smelting industries may be of particular interest. It is possible, on account of some inefficiencies in the smelting processes, for large quantities of metal to be released daily into the atmosphere and deposited in the soil and surface water over a radius of perhaps 15 km or more. It is well known, for example, that horses are sometimes killed by lead poisoning in areas surrounding a metal-smelting plant. Since most smelters are located in heavily populated areas or close to them, epidemiologic statistics based on large samples are available. The fact that water supplies and food are imported from other areas is of little consequence, because the exposure of the population to trace elements is overwhelmingly dominated by the presence of the smelting industry.

Maps to show the distribution of ore deposits are available for many countries, and maps of other areas are currently being prepared.

### **Selection of Trace Elements in Epidemiologic Studies of Cardiovascular Disease**

When studies on trace elements in relation to the etiology of a given disease are under discussion, a problem that frequently arises is which element should be analyzed in the tissues and in the environment? At present it is impossible to evaluate the relative importance of either major or trace elements in cardiovascular disease, since no multi-element data exist. Until evidence that will permit priorities to be assessed becomes available, all studies should ideally take as many elements as possible into consideration, even if the facilities of a particular laboratory permit the investigation of only a limited number. Since it is clearly essential that certain elements should be identified and studied in detail by as many laboratories as possible, the selection of these elements requires urgent and careful consideration.

An approach that seems to offer the best chance of success would be to analyze the major elements (particularly calcium, since its presence may influence the absorption of several trace elements), the essential trace elements, and those elements for which there is already some evidence of involvement in the development of cardiovascular disease. This latter evidence has been reviewed (Masironi, 1969; see also WHO/CVD/71.2) for cadmium, chromium, cobalt, copper, fluorine, iodine, lead, lithium, manganese, molybdenum, nickel, selenium, silicon, vanadium and zinc. The abundance of each of these elements varies greatly in water, soil, and various kinds of rock with which water comes into contact or from which soils are derived. Thus the trace element balance in the human body may be influenced both by food chains and the quality of drinking water.

However, an apparent correlation between the prevalence of a disease whose etiological factors are as yet unknown and some other variables, such as the occurrence and distribution of chemical elements, is by no means proof of a causal connection. Moreover, some

elements may accumulate at a particular site in the body because of the malfunctioning of an organ, but it does not follow that those elements are of importance in the pathogenesis of cardiovascular diseases.

Many elements may be important in this context, either because they interfere with elements whose physiological action is known, or because they have a physiological action of their own that has not yet been discovered. A practical approach to the identification of such elements would be to eliminate those that are unlikely to have any role in physiological functions for the following reasons:

(1) They are chemically inactive (i.e., Ar, Fr, He, Kr, Ne, Rn, Xe); obviously, elements that cannot participate in biochemical reactions are of no significance.

(2) They are produced artificially (i.e., Tc, Pm, and the transuranic elements).

(3) They are too radioactive (i.e., Ac, Pa, Pu, Np, Ra, Th, U); any physiological effects they might have would be overshadowed by their radiation effects, which do not pertain to the present type of study.

(4) Their occurrence is completely "dominated" by other elements with very similar physiochemical characteristics, which would,

therefore, disguise the physiological activity, if any, of the dominated elements; for example, Sc, Ga, and Hf are dominated by Al and Zr.

(5) They are practically unavailable to man, since they are very rare in the natural environment, are not usually found in biological systems, or have a very limited capacity for transference across membranes (e.g., Au, In, Ir, Os, Pd, Pt, Re, Rh, Ta, W, and the lanthanide series). It is necessary to show that the elements under study can enter the human system, otherwise their presence in the environment is of no importance.

By means of this approach, a list of trace elements that could usefully be studied in relation to cardiovascular disease can be drawn up to supplement the list of those previously reviewed (Masironi, 1969 and 1971). The list includes Al, B, Be, Bi, Br, Fe, Ge, Hg, Nb, Rb, Sb, Sn, Ti, and Zr. Several of these elements are known to enter the human system as a result of industrial pollution; this observation may be relevant on account of the apparent association that exists between the prevalence of cardiovascular diseases and industrialization. However, these criteria for selecting trace elements for investigation are empirical and should be considered only as the basis for a uniform approach to the problem.

## SUMMARY

Cardiovascular diseases are often found to be associated with certain physiochemical characteristics of the environment—namely, the hardness of the water and the types of rock and soil underlying the area. Regions supplied with soft water usually have higher cardiovascular death rates than do those supplied with hard water. Evidence linking cardiovascular diseases with

the geochemistry of rocks and soils is more limited. The nature of these associations is still speculative, but it is possible that certain trace elements are involved—some being beneficial and others harmful. Further epidemiologic studies are needed to identify these various trace elements.

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