Geochemical environments, trace elements, and cardiovascular diseases

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Cardiovascular diseases are often found to be associated with certain physicochemical characteristics of the environment—namely, the hardness of the water and the types of rock and soil underlying the area. Areas supplied with soft water usually have higher cardiovascular death rates than do areas 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 epidemiological studies to identify these various trace elements are desirable.

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.¹ 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 IN RELATION TO 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 (Mulcahy, 1966) and in others it was significant for women only (Björck 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, in the USA in Colorado (Morton, 1971) and Oklahoma (Lindeman & Assenzo, 1964), and in a province.

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"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 (International Classification of Diseases, 1965 revision, rubric 410–414) and its synonyms, e.g., coronary heart disease, myocardial infarction, atherosclerotic heart disease, and hypertensive disease (International Classification of Diseases, 1965 revision, rubric 400–404).
Table 1. Countries in which a negative association between cardiovascular mortality and water quality has been found

<table>
<thead>
<tr>
<th>Country</th>
<th>Study</th>
<th>Disease mortality group</th>
<th>Characteristics and main constituents of water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>Anderson et al. (1969, 1971)</td>
<td>coronary (sudden deaths only)</td>
<td>total hardness</td>
</tr>
<tr>
<td>Finland</td>
<td>Häskén (1970)</td>
<td>diseases of the circulatory system (clinical disability)</td>
<td>Ca, I, Br, Cl; specific conductivity</td>
</tr>
<tr>
<td></td>
<td>Karvonén et al. (unpublished data)</td>
<td>ischaemic heart</td>
<td>total dissolved solids; Ca, Mg, V, Mn, Fe, Sr, Zn, Br, Ti, pH</td>
</tr>
<tr>
<td>Ireland</td>
<td>Mulcahy (1966)</td>
<td>all cardiovascular disease (low significance)</td>
<td>total hardness</td>
</tr>
<tr>
<td>Italy</td>
<td>Marzot et al. (1968)</td>
<td>ischaemic heart (males only)</td>
<td>total hardness; total solids; alkalinity</td>
</tr>
<tr>
<td></td>
<td>Scassellati et al. (1971)</td>
<td>arteriosclerotic degeneration of the myocardium</td>
<td>total permanent and temporary hardness</td>
</tr>
<tr>
<td>Japan</td>
<td>Kobayashi (1957)</td>
<td>cerebrovascular</td>
<td>alkalinity CO\textsubscript{3}/SO\textsubscript{4} ratio</td>
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<tr>
<td></td>
<td>Kamiyama et al. (1969)</td>
<td>cerebrovascular</td>
<td>total hardness</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Biersteker (1967)</td>
<td>coronary (females only)</td>
<td>total hardness and calcium</td>
</tr>
<tr>
<td>Sweden</td>
<td>Biörck et al. (1965)</td>
<td>&quot;other&quot; degenerative heart, cerebrovascular (females only)</td>
<td>total hardness and calcium</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Morris et al. (1961), Crawford et al. (1968), Crawford et al. (1971)</td>
<td>all cardiovascular, cerebrovascular, coronary, and &quot;other heart.&quot;</td>
<td>total and temporary hardness; calcium</td>
</tr>
<tr>
<td></td>
<td>Hart (1970)</td>
<td>coronary heart</td>
<td>total hardness</td>
</tr>
<tr>
<td></td>
<td>Robertson (1968)</td>
<td>all cardiovascular</td>
<td>calcium; total hardness</td>
</tr>
<tr>
<td>USA</td>
<td>Schroeder (1960)</td>
<td>all cardiovascular, cerebrovascular, coronary, hypertensive heart</td>
<td>total hardness; calcium and magnesium</td>
</tr>
<tr>
<td></td>
<td>Muss (1962)</td>
<td>all cardiovascular disease in New York City</td>
<td>total hardness</td>
</tr>
<tr>
<td></td>
<td>Schroeder (1966)</td>
<td>coronary, cerebrovascular, hypertensive heart</td>
<td>total hardness; specific conductance; dissolved solids; K, Mg, Si, HCO\textsubscript{3}, Cl, Na, SO\textsubscript{4}, Ca, V, Ba, Sr, Li, beta-radioactivity</td>
</tr>
<tr>
<td></td>
<td>Dudley et al. (1969)</td>
<td>coronary heart (in warm and temperate areas only)</td>
<td>total hardness</td>
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<tr>
<td></td>
<td>Peterson et al. (1970)</td>
<td>coronary, hypertension (sudden deaths only)</td>
<td>total hardness</td>
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<tr>
<td></td>
<td>Masironi (1970)</td>
<td>all cardiovascular disease, hypertensive heart</td>
<td>total hardness; alpha-radioactivity; Cr, V, Zn, Mn, Fe</td>
</tr>
<tr>
<td></td>
<td>Sauer et al. (1971)</td>
<td>cardiovascular-renal, coronary</td>
<td>total hardness; total dissolved solids; Ca, Mg, Na, K</td>
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<tr>
<td></td>
<td>Groover et al. (1972)</td>
<td>cardiovascular-renal</td>
<td>total hardness</td>
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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. Favourable changes in cardiovascular mortality rates were found in areas where the water had been hardened, and unfavourable 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 studies in the United Kingdom a comprehensive search was made for social or environmental factors that might correlate with water hardness or calcium, but none was found; rainfall was the only closely associated variable; this would be expected since the high-rainfall areas
are mostly the soft-water areas. In 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 & Crawford (1967) compared the prevalence of coronary and myocardial disease in soft- 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) that the higher death rate from ischaemic heart disease in the soft-water areas in 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, and this is found also in 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 in 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 in several studies with mortality. 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 & McCance, 1943; Murray & Wilson, 1945; Hollingsworth, 1956).

Longer QT intervals in the ECG, which entail 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 & Goldsmith, 1966).

Calcium and magnesium are vitally involved in enzyme systems in the myocardium and in maintaining the electrolyte balance, and derangement 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 elec-
lyte balance could be delayed, water lacking calcium and magnesium, and thus favouring 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 & 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 favourably 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 (Hässänen, 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 & 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 from the disease (Bala & 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.1 The suspected effect of soft water in relation to cardiovascular disease could therefore be explained by the absence of certain "protective" elements or by the presence of certain "harmful" elements extracted from distribution pipes. Unfortunately, studies to compare concentrations of trace elements in soft and hard water (Schroeder, 1966; Masironi, 1970; Boström & Wester, 1967; Crawford & Morris, 1967; Crawford et al., 1968) have not produced consistent results.

1 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).

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 IN RELATION TO GEOCHEMICAL ENVIRONMENT**

Relationships were found between cardiovascular diseases and the composition of both drinking water and raw water (Kobayashi, 1957; Hässänen, 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 the USA in Georgia and North Carolina cardiovascular disease death rates are highly associated with the types of soil, 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). These rocks consist mostly of 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 be relatively poor in trace elements. The soils, however, are comparatively rich in trace elements. An 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 be relatively rich in trace elements. The relative abundance of trace elements in water in these two areas of contrasting cardiovascular mortality rate 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 available for solution in water.

On the other hand, preliminary data (Masironi, 1971) suggest that cardiovascular death rates may be higher in some areas overlaying 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., 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 soils, the upper layers of which have been leached. These observations are consistent with the pattern 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 north-eastern Finland, where death rates for 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 and water may extract larger amounts of minerals from these soils.

It seems, however, that relatively high cardiovascular mortality rates can be found also in areas that are situated on very young formations, i.e. Quaternary deposits less than 1 million years old. Countries (e.g., Hungary and Romania) that lie predominantly on these young formations have higher cardiovascular death rates than neighbouring 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 Piedmont and the Po Valley in Italy; these regions have the highest cardiovascular disease death rates in the respective countries. Similar trends can be detected also in the USA; some counties in Louisiana and Arkansas (Mississippi Valley) and 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 epidemiological relationships between death rates from cardiovascular diseases and water quality on the one hand, and the geochemical environ-

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1 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 temperate 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.

ment on the other, 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 (i.e., 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. It is frequently saline.

The further classification of natural water is usually based on 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 earths 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 the principal ions. Various mathematical and graphical 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 solubilities of the minerals that form limestone. Water from granitic terrain, on the other hand, tends to be soft, mainly as a result of the presence of sodium-rich minerals 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 are more varied in composition than igneous rocks are; this is reflected in the more variable characteristics of water associated with this type of 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., 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 the mineral composition and on the depth from which the water is taken. This type of water typically contains calcium–magnesium, carbonate, and hydrogen carbonate ions. The magnesium originates mainly from the mineral dolomite, which is a main constituent in the rock type of the same name. Dolomite also occurs in varying proportions in limestone rock.

Atmospheric water charged with carbon dioxide percolating into siliceous rocks attacks preferentially 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 ion. 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 ON 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, vegetation, animals, and finally, through 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 cycle 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", alter the natural migration and distribution of elements. As a result of these complicating factors, and because of limitations in the mortality and morbidity data, correlations between geochemistry and cardiovascular disease are unlikely to be seen during cursory investigations. Nevertheless, some consideration of the general geological and geochemical characteristics of epidemiologically contrasting areas may provide some indications for further study. Conversely, observations of the epidemiological characteristics of areas that differ in their geology and geochemistry may also yield information useful in 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 for cardiovascular diseases; (2) areas with leached soil and those with relatively unleached soil should be compared; (3) mining and other industrial areas where the population is exposed to higher than normal amounts of certain trace elements should be studied to determine the health aspects of the presence 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 supplies of food and water are generally brought in from a distance and 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 epidemiological data. An advantage of investigating areas with a relatively low population density is that the people (farmers, etc.) generally have a close relationship to the land and tend to consume food that is produced locally and water from wells or springs.

Epidemiological studies in geologically contrasting areas

The first source of data for environmental geochemistry is a good geological map showing the distribution and conformation of geological structures. Other important sources of information are analyses of various types of rock; tables of geochemical data are available for many regions that may be of epidemiological 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 rocks, soils, 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. In sedimentary rocks the elements mentioned above, except calcium, are less concentrated in sandstones and, except calcium, magnesium, and manganese, 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, or even to a single element, of particular importance. In this event, geological studies could be restricted to particular types of rock differing widely in their chemical composition. Meanwhile, investigations of cardiovascular epidemiology in relation to the geochemistry of the area will probably continue to implicate different
elements or groups of elements in either beneficial or harmful effects on 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 epidemiological data. Therefore, comparisons of areas overlying shale with areas overlying sandstones may be more easily made since large areas are known that lie mainly over one or other type of rock. A difficulty is 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 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 inevitably a difference in the abundance and availability of trace elements, the correlation of epidemiological data with the age of the rock in various study areas could be a first step in extending this kind of investigation on a worldwide scale.

Another useful approach might be to compile health data by 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 mineralogical composition.

A generalized soils 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 of increasing tendency to be depleted of trace elements that were originally present in the parent materials: desertic (arid) soils, tundra soils, chernozemic soils, podzolic soils, and latosolic soils. A sixth type, mountain soils, 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 charac-

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1 See footnote on p. 143.
teristically 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 the trace elements that have been linked with cardiovascular diseases occurring 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 a water-soluble form will be approximately related to the degree of leaching. The collection of epidemiological 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 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 & Webb (1962), zinc is present in ore deposits in concentrations of 80,000 ppm (8%) 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; vanadium, 300. Many of the elements of interest in relation to cardiovascular diseases also occur as minor constituents of ores of other metals but are nevertheless present in much greater quantity than in the common rocks, and 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 ores are mined and the metal extracted. The epidemiological 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 close to or in heavily populated areas, epidemiological 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 others are currently being prepared.

Selection of trace elements in epidemiological 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 analysed 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 a limited number only. 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 analyse 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 that they are involved in the development of cardiovascular disease; this evidence has been reviewed (Masironi, 1969) 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 the soils are derived. Thus the trace element balance in the human body may be influ-

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1 See also Report of a meeting of investigators on trace elements in relation to cardiovascular diseases, Geneva (unpublished document WHO/CVD/71.2).
enced 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 connexion. 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 belong to the present type of study;
4. their occurrence is completely "dominated" by other elements with very similar physicochemical 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, additional to those previously reviewed (Masironi, 1969), that could usefully be studied in relation to cardiovascular disease, can be drawn up; 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 the degree of industrialization.

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.

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1 See also footnote on p. 143.

RéSUMÉ

MILIEUX GÉOCHIMIQUES, OLIGO-ÉLÉMENTS ET MALADIES CARDIO-VASCULAIRES

On a découvert l'existence d'une relation entre la prévalence des maladies cardio-vasculaires et les variations de la teneur en oligo-éléments des tissus et liquides de l'organisme. On a pu aussi établir un lien entre la mortalité due à ces affections et certaines caractéristiques géochimiques et hydrologiques de l'environnement, comme la nature des roches et des sols et la dureté de l'eau. L'étude de ce dernier facteur en particulier montre que dans les régions disposant d'eau (de boisson ou autre) douce, les taux de mortalité par maladies cardio-vasculaires sont quasi uniformément élevés. L'inverse s'observe dans les régions caractérisées par une plus grande dureté de l'eau. On ne constate, par contre, aucune corrélation stable entre la dureté de l'eau et la prévalence d'autres affections ou d'autres variables mésologiques et socio-économiques.

On peut prêsumer que l'action bénéfique de l'eau dure est due à la présence d'éléments favorables, alors que l'eau douce devrait sa nocivité à certains éléments dangereux comme le cadmium et le plomb provenant des tuyauteries. Quant à nos connaissances des liens unissant la mortalité par maladies cardio-vasculaires et la nature du milieu géochimique, elles sont encore très limitées. Il semble que dans certains pays les taux soient plus élevés dans les régions où la couche rocheuse sous-jacente est constituée de formations très anciennes datant de l'ére précambrienne.

On peut admettre que la nature des oligo-éléments
Les caractéristiques chimiques du milieu se modifient. Les activités industrielles, notamment, provoquent des changements subtils de l'équilibre des oligo-éléments qui peuvent, par l'intermédiaire de l'eau, de l'air et des chaînes alimentaires, affecter la balance des sels minéraux dans l'organisme humain. On sait que les oligo-éléments jouent un rôle très important dans nombre de fonctions physiologiques, dont très probablement la fonction cardio-circulatoire. On conçoit dès lors qu'un déséquilibre de ces substances persistant toute la vie dans l'organisme puisse entraîner finalement l'apparition de maladies cardio-vasculaires ou d'autres affections chroniques.

Des facteurs nombreux et complexes déterminent la présence et l'abondance des oligo-éléments dans le milieu naturel. Il est difficile d'obtenir des informations à ce sujet par la simple étude géologique des sols et rien ne peut remplacer les investigations géochimiques spécialement conçues pour mesurer sur place les quantités d'oligo-éléments réellement présentes dans les roches, les sols, l'eau, les plantes et les tissus.

Les auteurs suggèrent quelques domaines où de telles études géochimiques en rapport avec l'épidémiologie des maladies cardio-vasculaires pourraient être entreprises: régions d'âge géologique différent et ayant subi l'action des eaux avec une intensité variable; zones minières où la population vit probablement dans un milieu contenant de fortes concentrations d'oligo-éléments. On ne peut certes envisager une étude de l'ensemble des oligo-éléments et on propose de la limiter à ceux dont l'analyse présente un intérêt particulier pour la pathologie cardio-vasculaire.

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