TRACE ELEMENTS AND EPIDEMIOLOGY*

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In the one hundred years since the birthday of Academician W. J. Vernadsky, in whose honour this Geochemical Conference is being held, the population of our world has grown from about 1,250 million to not far short of 3,150 million, an addition of some 1,900 million persons. Thus, there are approximately two and one half times as many people in the world today as there were when Academician Vernadsky was born. Furthermore, in many parts of the world people live longer today than they did one hundred years ago. Thus it is not surprising that, partly as a result of greater medical knowledge, and partly because man now tends to live longer, and in places where formerly he did not live, today different diseases are demanding priorities in research than was the case one hundred years ago. Today we know the causes of such diseases as malaria, tuberculosis, cholera, typhus, and typhoid; we have merely to apply our knowledge. At present we face a new series of afflictions including coronary diseases, cancers, and equally challenging but less publicized ones, such as multiple sclerosis, a disease that was barely recognized one hundred years ago. I believe that geochemistry has an important role to play in determining the causes of some of those diseases which give most concern in the world today.

Man has always been interested both in his health and in the world around him. Thus it was to be expected that medicine and geography, two of the earliest fields of learning to develop, should be combined in epidemiological investigations.

Geochemistry, as it is understood today, is a comparatively new

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science, and it has not had time fully to develop effective links with all its sister sciences. V. M. Goldschmidt (1954) wrote, " The very great importance of biochemical processes in geochemistry was recognized especially by Russian scientists, such as J. W. Samoilov, and in particular by W. J. Vernadsky, followed by A. E. Fersman, and A. P. Vinogradov ". Thus it would seem fitting that at this celebration, and in the presence of Academician A. P. Vinogradov, an attempt should be made to indicate how there may be increasingly fruitful co-operation between geochemists, who are comparative newcomers to the scientific world, and medical researchers who may boast of a long history of organized effort.

During the past one hundred years our knowledge of hormones, vitamins, bacteria, viruses, and enzymes, has grown greatly. We recognize that all may, on occasion, play a part in determining the health of vegetal and animal life and, furthermore, we know now that all may be stimulated, poisoned, or affected in one way or another by various combinations and concentrations of specific elements. There is general agreement that although geographic factors such as topography, climate, and weathering influence trace element distribution patterns, the trace elements that find their way into our water, soil, and food, originate in the rocks of the earth's crust, and it is in the chemistry of the rocks of the earth's crust that geochemistry is primarily concerned.

Geochemists are interested in trying to understand the reasons for the varying concentrations of the trace elements in different parts of the earth's crust, and in mapping these different concentrations. Apart from a few notable exceptions, epidemiologists have been recording medical data on maps where political and geographic boundaries have usually formed the terms of reference.

In the material which follows, the author attempts, by citing some recent investigations, to illustrate how geochemical and medical knowledge can be integrated advantageously.

Lead and Disease

The danger of gross lead poisoning has long been recognized, so much so that, in most countries, laws have been passed to protect men and women from excessive exposure to this element. However, every year in British Columbia, some cattle find some lead, usually in the form of discarded storage batteries, sample them, and die of lead poisoning.

What is not so generally realized is that lead may well play some part in such diseases as cancer, and multiple sclerosis. Brieger and Rieders (1959) write—" of great importance and significance at present are reports that excess lead absorption leads to hypertension, nephrosclerosis, and general arteriosclerosis ". The same workers refer to observations by Vigdortchik, who has reported on an increased incidence of hypertension and nephrosclerosis in Russian workers.

Lead has been investigated by several workers as a possible cause of multiple sclerosis, but no relationship has ever been proved. During the past five years, we have assembled many new data, and consider that the ideas put forward by Cone (1934), Campbell (1950), and Swank (1950) should be re-examined.

Although fully appreciative of the fact that cancers embrace a host of diseases, and that there are doubtless many factors which can initiate the disease, the fact remains that lead must be considered as one potential cause. In this connection Dr Boyland (1960) of the Chester Beatty Research Institute, graciously summarized researches on lead as follows:

> The carcinogenic action of lead salts was first shown by Zollinger, Virchow's *Arch. path. Anat.*, 1952, **323**, 694. This finding has been repeated and extended, using other lead salts and other routes of administration, by van Genderen, and van Esch in Holland, by Walpole and Williams in Manchester, and by ourselves in this laboratory. All these workers have found that the administration of lead to rats induces cancer of the kidney. Until now, the doses of lead employed have been quite large.

Having had medical evidence that lead may well be responsible for some cancers, and that it may have some connection with multiple sclerosis and other diseases of a degenerative nature, it appears that a review of some aspects of the geochemistry, and more particularly the biogeochemistry of lead is justified.

Geochemistry of lead

In a previous paper, Warren and Delavault (1960), we have reviewed some of the general data available concerning the lead content of rocks and soils. Goldschmidt (1954a), Vinogradov (1959), Borchert (1959), Wedepohl (1956), Mitchell (1946, 1948), Swain (1955) Swain and Mitchell (1960), and Launamaa (1956) have, between them, provided a wealth of background information.

For the purposes of this paper, it is sufficient to say that whatever analytical methods are used, one cannot but be impressed with the occasional wide deviations from what is generally considered normal in the lead content of some rocks. It is correct to say that each type of rock tends to have a " normal " lead content, but it is equally important to know that there are wide variations in the lead content of eruptive rocks, which superficially resemble one another closely, and that in a sandstone or limestone formation one particular facies may contain as much as one hundred times its usual quota of lead. Lounamaa, in the publication which is mentioned above, wrote—" Lead differs from all the afore-described elements in that the soil samples from the different outcrops invariably contain more of it than do the rocks. The strong enrichment of lead into the soils overlying silicic rocks is quite remarkable ". Other workers have also noticed the manner in which lead may be concentrated in some soils. In our experience, lead tends to be more concentrated in forest than in grassland soils, other factors being equal.

However, although the lead content of rocks and soils is vital, for the sake of space, fuller discussion is omitted, and we turn next to the biogeochemistry of lead, which aspect would seem to be most intriguing to medical men.

Biochemistry of lead

During the past ten years, Lounamaa (1956), Cannon (1960), Schroeder (1961), and Kehoe (1961), amongst others, have added much to our knowledge of the lead contents of various plant and animal organs.

The medical workers, Schroeder and Kehoe, record the lead content of vegetal matter including food stuffs, and report much the same amounts and variations as the botanist, Lounamaa, and the geologist, Cannon. Although Schroeder reports the contents of " wet " samples, and Kehoe some " wet " and some " dry " samples, and Cannon and Lounamaa give contents of lead in ash, the lead contents reported are all of the same general order of magnitude. On the basis of 1908 samples of grasses, herbs, and the leaves of shrubs, deciduous trees, and conifers, Cannon gives an average lead content in ash of seventy parts per million. On the basis of 819 samples, which included lichens, mosses, ferns, conifers, deciduous trees and shrubs, dwarf shrubs, and grasses and herbs, Lounamaa reports comparable results and notes that twigs tend to contain more lead than do the leaves and needles. Incidentally, he used two years of growth for his samples. In our own prospecting work we have encountered significant variations in the lead content of young growth during a growing season. The variations are great enough to make it advisable to take only the previous season's growth when sampling in a prospecting programme.

Perhaps we may sum up the present state of our knowledge of the biogeochemistry of lead by saying that, normally, the ash of most recent vegetation contains from 50 to 100 parts per million of lead, and that of growth of the previous year from 25 to 50 parts per million. However, what is important is the fact that where vegetation grows over soil or rock anomalously rich in lead, it may well contain more than 1,000 parts per million of lead. Lounamaa has reported as much as 3,000 parts per million in birch (*Betula verrucosa*) and alder (*Alnus incana*). We have found stems of a previous year's growth of birch (*Betula glandulosa*) carrying 2,500 parts per million of lead.

Unfortunately, vegetation may acquire lead, not only from soil because of that soil's geological origin, but by contamination from such sources as chemical sprays, smelter fumes, or automobile exhausts derived from burning " leaded " gasoline.

At an early stage in our investigations, with the help of some friends who collected samples for us, we assembled plant ash from three centres exposed to varying concentrations of automobile exhaust, and also from control areas which could be said to represent normal backgrounds. The results appear in table I. Dr M. Salmi had check analyses on the Helsinki samples run by spectroscopic methods: the other analyses were made by our routine prospecting techniques.

Usually vegetal matter used as food has been found to contain much less lead than shrubs and forest trees growing wild. Whether this is a matter of plant ecology, whether it is a result of natural selection, or whether it merely represents an impoverishment of a cultivated soil, we do not know. Perhaps other workers can supply the evidence necessary to elucidate this problem.

To sum up, it may be said to be established that:

1. Different organs of vegetal matter pick up widely different amounts of lead.
2. Similar organs of different age have different concentrations of lead.
3. Different species of trees and lesser plants pick up widely varying amounts of lead, even though they are growing on soils containing identical amounts.
4. Vegetal matter used as food tends to contain much less lead than other vegetal matter of the same age.

Because of the inherent difficulties of evaluating results expressed variously as parts per million of lead in " wet ", " air-dried ", and " oven-dried " samples, the remainder of these remarks, except where indicated otherwise, will refer to parts per million of leadi ash.

TABLE I

LEAD CONCENTRATIONS IN VEGETATION EXPOSED TO DIFFERENT CONCENTRATIONS OF AUTOMOBILE EXHAUSTS

(Lead expressed as p.p.m. in air-dried matter. Lead in ash in brackets)

Species of tree	*Locality London, England*		*Control from country nearby (1st year stems)*		
A					
Lime	5	(50)	0.4	(8)	(London samples
Yew (needles)	6	(100)	0.4	(7)	—kindness of
Willow	2	(30)	1.0	(35)	T. Deans)
Birch	8	(160)	1.0	(36)	
Oak	20	(280)	0.8	(30)	
Ash	14	(160)	2.0	(30)	
Hazel	52	(680)	2.0	(50)	
B	*Brussels, Belgium*				(Belgian samples
Oak leaves	21	(930)	0.3	(12)	—kindness of
Beach leaves	17	(690)	1.6	(51)	J. Jedwab)
C	*Helsinki, Finland*				(Finnish sample
Maple leaves	19	(160)	4	(40)	—kindness of
Maple twigs	9	(160)	3	(100)	M. Salmi)
C	*Helsinki, Finland*		(Check analyses by spectroscopy)		
Maple leaves	28	(240)	1.5	(16)	
Maple twigs	13	(230)	1.0	(37)	

As is true for trees and lesser plants, weather, climate, season, and doubtless many other factors, affect both the lead and the ash content of oven-dried edible portions of cereals and vegetables. Potatoes seem to vary appreciably from other vegetables in the content of their ash.

Solely as a working hypothesis, table II is given. It is hoped that, before long, other workers will provide more abundant and precise data.

However, just as under special conditions the ash of trees and lesser plants may carry anywhere from 5 to 50 times its normal quota of lead, so also may vegetables and cereals. Some time ago we drew attention to the fact that some foods were much higher than normal in lead, Warren and Delavault (1962), and more recently Cannon and Bowles (1962), have drawn attention to veget-

TABLE II

SUGGESTED " NORMAL OR AVERAGE " AND " USUAL RANGE " FOR LEAD IN EDIBLE PORTIONS OF FOOD

Lead expressed as p.p.m.

	A. In oven-dried material		*B. In ash*		*(Ash content of oven-dried food)*	
	Normal	*Usual Range*	*Normal*	*Usual range*	*Normal*	*Usual range*
					Per cent	*Per cent*
Vegetables ..	0.35	0.10–0.50	4	2–25	10	5–20
Cereals ..	0.35	0.20–0.50	9	4–25	4	3– 5
Potatoes ..	0.07	0.05–0.10	2	1–15	4	3– 6

ables which contained in their ash as much as a fearsome 1,000 p.p.m. of lead with 16 samples averaging 115 p.p.m.!

Lead and cancer

Allen-Price (1960) has recently described the uneven distribution of cancer in west Devonshire, and co-operated with the author when a collection of rocks, soils, and food samples were made.

In west Devonshire the mortality from cancer is, on a twenty year average, 16.5 per cent. This mortality rate is close to the average for England and Wales, and, if Allen-Price had not investigated much more closely, nothing unusual might have been discovered about the distribution of cancer cases in this area. Fortunately, Allen-Price plotted all deaths occurring during a twenty year period on an ordnance survey map. Deaths from cancer were marked by a cross, and those from other diseases by a circle. Allen-Price then noted: " The extraordinary distribution of the disease then became apparent. For example, in one hamlet the ratio of crosses to circles is one in twelve, whilst in an adjoining hamlet of a comparable community, the ratio is one in three ".

After examining every other factor that might be considered responsible, Allen-Price came to the conclusion that water and geological formations must be the cause of the unusual distribution of cancer cases. Allen-Price summed up: " Certain facts support the hypothesis that cancer in this area is indissolubly connected with water supplies: the distribution is beyond dispute, being derived from the actual death certificates; the geological formations are unquestionable; and the visual and statistical evidence for the distribution, as recorded in maps and tables, cannot be questioned ".

We have now examined rock, soil, and food products from many parts of Cornwall, Devonshire, and Sussex. It would have been gratifying to be able to report that all the gardens associated with high cancer mortality were high in lead, and that those associated with low cancer mortality were low in lead. Alas, such does not appear to be the case.

Nevertheless, some exciting and seemingly pertinent facts have emerged from these studies. They may be summed up as follows:

1. In Sussex where, according to Howe (1961), malignant neoplasms of the stomach are well below the average for England and Wales, soils commonly run less than 20 p.p.m. of sulphuric acid extractable lead, rocks contain less than 5 p.p.m. aqua regia extractable lead, and trees 50 p.p.m. or less of lead.

2. In Devon and Cornwall, however, the facts are different. Most rocks also contain less than 5 p.p.m. of aqua regia extractable lead, but a few have more than 10, and in rare places, more than 50.

As might be anticipated many soils, actually between forty and fifty per cent of our samples, show what we consider a normal content of sulphuric acid extractable lead, namely, less than 20 p.p.m. However, nearly twenty-five per cent contain 100 p.p.m. or upwards, and a small percentage actually run better than 1,000 p.p.m., and some of the highest, apparently, can be correlated with some of the high cancer areas encountered by Allen-Price.

All west Devon vegetables which we have had for analysis, have carried anomalously high amounts of lead, never less than 10 p.p.m. in ash, but two samples, one of gooseberries and one of lettuce, from high cancer areas, carried 250 and 300 p.p.m. respectively.

It may or may not be coincidence, but Dr H. Cannon tells us that in routine geochemical investigations, similar results have been encountered in one district in the U.S.A. where the incidence of cancer has been considered high. Furthermore, Howe (1962) has, in one epidemiological study in Wales, " tended to implicate lead-zinc polluted water in the causation of gastric cancer ".

Fortunately we have independent evidence that there are anomalously high amounts of lead in some of the soils and plants of this area. Millman, working in eastern Cornwall (1953), has found not only that some leaves and young stems of oak (*Quercus sp.*), birch (*Betula sp.*), ash (*Fagus sp.*), and willow (*Salix sp.*), have many hundreds of parts per million of lead in their ash, but also that a few samples carry well over one thousand parts per million. Moreover, Millman also reports that, although most of the 103 Cornish soils he sampled ran from ten to thirty parts per million of lead, there were three which ran one hundred parts per million. Incidentally, Millman's results were obtained by spectroscopic analyses, and ours by chemical methods.

In short, three different workers in three different areas have found inconclusive, but decidedly suggestive evidence that some cancers and lead may be related.

Unfortunately, much useful information concerning the distribution of cancer, and particularly stomach cancers, including valuable reports from the U.S.S.R. (Chaklin 1962), Great Britain (Howe 1961), and elsewhere, appear largely, if not entirely against political divisions, In British Columbia, cancer statistics are prepared against a background of school districts. Whatever the cause, or causes, of cancers, may be, whether it be abnormal genes or some peculiar virus, one thing is sure: school districts are not likely to provide the clue that is so eagerly being sought. Is it not worth while attempting some studies along the lines tried by Allen-Price? Could not appropriate cancer cases be plotted against biogeochemical provinces as defined by A. P. Vinogradov and D. P. Malyuga (1957)? In areas where this treatment is not practical, possibly simple geochemical provinces might be used for epidemiological studies. The results might be most useful!

Lead and multiple slcerosis

Some years ago I published a brief note on " Geology and Multiple Sclerosis " (Warren, 1959). In this note, attention was drawn to the fact that in several areas the prevalence of multiple sclerosis was known to be high, and yet, in closely related geographic areas, the prevalence was comparatively low.

In Møre og Ramsdal in Norway (Allison, 1963), and in the Outer Hebrides of Scotland (Sutherland, 1956) evidence points to a much lower prevalence of multiple sclerosis than there is in the geographically similar areas of Vestfold in Norway, and the Orkneys and Shetlands of Scotland (Sutherland, 1956). Geochemists generally would agree that the old gneisses which underlie the Outer Hebrides and Møre og Ramsdal areas are normally low in lead, whereas the rocks in the Vestfold area contain potash felspars comparatively rich in lead, (Heier and Taylor, 1959). Moreover, this latter district almost certainly has had deposited over it glacial debris derived from Nordmarkites of the Oslo area, and possibly even some lead from the mineralization around Grua. The Orkneys and Shetlands contain many beds of " Old Red Sandstone ", a formation known to contain, at least in some localities in the British Isles, some facies high in lead.

In Sweden, from *Acta Medica Scandinavica* (1942), we learn of three areas where the prevalence of multiple sclerosis is remarkably low. These areas are (*a*) Gavleborg, North of Gavle, (*b*) Sodermanland Province, south and west of Stockholm, and (*c*) large coastal sections of Halland, Goteborg, and Bohus provinces. Is it likely to be mere coincidence that these three areas are all predominantly underlain by old gneissic rocks comparable in age and habit to those found in the Hebrides and in Møre og Ramsdal?

From the same source given just above, we learn that six areas have a greater than normal prevalence of multiple sclerosis. They are as follows:

Northern Västergotland
Northwestern Ostergötland
Near Stockholm and Uppsala
Malmöhus
South Jamtland and North Harje-dalen
Vasterbotten

Once again it would seem unlikely to be accidental that each of these areas has some direct and well known association with lead. Northern Västergotland, and Northwestern Östergötland are in an area which contains Cambrian rocks that only recently have been shown by Cobb and Kulp (1961), to contain significant amounts of lead, and furthermore two mineral areas lie near the northern end of Lake Vattern in the latter area. In the area just west of Stockholm and Uppsala lie some of the the best-known lead occurrences in Sweden. In Malmohus, there is a large area of Eo-Cambrian rock which may be considered as a potential lead carrier. South Jamtland, and North Harje-dalen not only lie within one of the greater concentrations of Eo-Cambrian rocks occurring in Sweden, but also contain at least two lead mines, as well as some of the best agricultural land in Sweden, Eklund (1955). Vasterbotten lies to the southeast of the Great Boliden mineral area which, amongst its many metals, does contain lead, and this lead would surely be brought by glaciation to those areas on the coast where the prevalence of multiple sclerosis is high.

In England, and Northern Ireland, there are several localities where the prevalence of multiple sclerosis has been high enough to attract medical attention, and, in some instances, provoke scientific articles. Eight such areas have been drawn to my attention, and in 1960, visits were made to five of them, two in Gloucestershire, one in Somersetshire, and two in Northumberland. Samples of rock, soil, and food products were collected and analysed in our laboratories by routine prospecting methods. Thanks to the kindness of the Macaulay Institute of Soil Research at Aberdeen, the food products were ashed before being shipped to Canada. In every instance, these rock, soil, and food samples were found to contain anomalous amounts of lead, usually of the order of from two-and-one-half to ten times what is considered to be normal.

Of the other three localities one is in Cornwall, one in Northern Ireland, and the other in Derbyshire. The Derbyshire locality is in an area famous for its lead mines. In Cornwall, Dr E. R. Hargreaves, the deputy county medical officer, collected some soil and vegetable samples, and a preliminary report suggests that the lead content of both vegetable and soil samples is high: as a precaution, repeat analyses are being carried out before further comment is made. From Northern Ireland, Dr R. S. Allison sent some dozen soil samples from gardens of multiple sclerotic patients. These soils tended to contain only slightly more than average amounts of lead. However, one soil did run thirty parts per million of sulphuric acid extractable lead, an amount at least three times normal.

In Canada, there are several areas where a relatively high prevalence of multiple sclerosis is suspected. It must be emphasized that, except for one or two areas which have been critically investigated, there simply are no reliable statistics in Canada concerning the prevalence of this disease.

As a result of our investigations, several interesting and seemingly relevant facts have emerged.

First, in two provinces raw maple sugar has been discovered with such a high lead content that it had to be diluted with low lead bearing material before it could be considered safe for distribution.

Second, in south western Ontario there are rocks with many times their normal quota of lead, and these have resulted in the production of some grain with an abnormally high lead content, Warren and Delavault (1961).

Third, thanks to grand geochemical studies by the Geological Survey of Canada, and most cordial co-operation from officials of the Nova Scotia Department of Agriculture, it is possible to say that there are some soils and food products in Nova Scotia with abnormally high lead contents. It is generally considered that there are some "pockets" in Nova Scotia where the prevalence of multiple sclerosis is high.

Fourth, studies which are being carried on at the present time, and which are therefore incomplete, suggest that, although the great majority of the soils and vegetal matter of Central Canada have normal lead contents, there are exceptions. It is these exceptions that are likely to prove interesting.

Fifth, we have found two districts in Canada where soil and/or vegetation are abnormally high in lead. Diligent inquiry has revealed the information that probably the prevalence of multiple sclerosis in these districts is as high, or higher, than in any other part of the world. Today we are trying to arrange for competent neurologists to make a detailed study of these areas. If the information that we have collected were to be confirmed, surely the data would be significant.

Summary and Conclusions

In the past hundred years, there has been a great increase in the world population, and, in many parts of the world people are living longer. As a result of these factors, and of advances in medical knowledge, the world is faced with a change in emphasis concerning the diseases which challenge mankind. Many of the more prevalent diseases of today are known to be, or suspected of being, related to vitamin, hormone, viral, bacterial, or enzyme imbalances, and these, in turn, may well in some instances at least, be related to element imbalances, and particularly trace element imbalances.

Geochemists have recognized, and been interested in trace element distribution patterns on the earth's crust and some, led by Vinogradov and Malyuga, have recognized the presence of biogeochemical provinces.

Facts have been brought forward, not to prove that lead was the the cause of some cancers and multiple sclerosis, but to demonstrate that there is evidence that this assumption might well be taken as a working hypothesis. Should other independent workers confirm and extend the facts which we have assembled, then it would surely be possible to initiate specific medical research that would prove, or disprove, the validity of any hypothesis linking lead with multiple sclerosis and some cancers.

In diseases where trace elements may be involved, it would appear to be an unnecessary dissipation of effort to make epidemiological studies against a background such as school districts, state, or urban boundaries which only fortuitously could have any trace element significance.

Co-operation between medical and geochemical researchers might also avoid some unnecessary work. The diet of city people is apt to be extremely complex, and attempts to determine trace element intakes are costly and frustrating. On the other hand, there are still many areas in the world where people are obtaining much of their sustenance directly from one geochemical province, and where correlations between disease and geochemical patterns may well prove to be rewarding. In medical geochemical investigations, international co-operation would probably provide many useful and unanticipated dividends. The application of geochemical knowledge relative to the dispersal of trace elements in the earth's crust, should greatly further the potentialities for profitable epidemiological investigations.

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ON AIRS, WATERS, AND PLACES

" 1. Whoever wishes to investigate medicine properly, should proceed thus: in the first place to consider the seasons of the year, and what effects each of them produces ... Then the winds, the hot and the cold, especially such as are common to all countries, and then such as are peculiar to each locality. We must also consider the qualities. In the same manner, when one comes into a city to which he is a stranger, he ought to consider its situation, how it lies as to the winds and the rising of the sun; for its influence is not the same whether it lies to the north or the south, to the rising or to the setting sun. These things one ought to consider most attentively, and concerning the waters which the inhabitants use, whether they be marshy and soft, or hard, and running from elevated and rocky situations, and then if saltish and unfit for cooking; and the ground, whether it be naked and deficient in water, or wooded and well watered, and whether it lies in a hollow, confined situation, or is elevated and cold; and the mode in which the inhabitants live, and what are their pursuits, whether they are fond of drinking and eating to excess, and given to indolence, or are fond of exercise and labour, and not given to excess in eating and drinking."

The Genuine Works of Hippocrates
Francis Adams, 1849, Vol. 1, p. 190