Meetings

Medical Geology and Geography

Nobody suffering from any particular disease should look to trace elements for a wonderful new cure in the immediate future; trace elements, although probably important, are not the only factor pertinent to the health of plants and animals. Nevertheless, there is much evidence suggesting that a relation between trace elements and human health may be much more than a fascinating hypothesis. The manners and routes by which trace elements progress from rock to soil and thence to plants, animals, and humans are diverse, complex, and little understood. Trace elements are the warp and woof of Earth's crust, and there is increasing evidence that many of them are essential to both healthy and unhealthy living tissue in plants and animals. The whole question warrants much more intensive investigation.

These points were emphasized by the panel of an interdisciplinary symposium on the subject, "Medical geology and geography"; the symposium (Montreal, 28 December 1964) was sponsored by the geology and geography (E) and agriculture (O) sections of the AAAS and by the Geochemical Society. The four panel members, a chemical biologist, a professor of pharmacognosy, a geologist, and a general medical practitioner (in the order in which papers are reported), each had a special interest in trace elements and was convinced that research will soon pay dividends. Their views were remarkably complementary.

The theme of Arthur Furst (University of San Francisco) was that metals, both essential and nonessential, may play a more vital role in the cancer process than has been heretofore recognized. "In addition to the known phenomenon of metal carcinogenesis, it is possible to postulate that the mechanism of action of both carcinogenic compounds and antitumor agents can conceivably follow a pathway that requires chelation or metal-binding."

Close to 40 elements found in living tissue may be classed in three groups; there is no sharp demarcation line between groups, and new knowledge is constantly changing the grouping:

1) Bulk elements comprise the bulk of living tissue; they are hydrogen, carbon, nitrogen, oxygen, sodium, magnesium, phosphorus, sulfur, chlorine, potassium, calcium, and iron. Iron is included for those species that contain hemoglobin.

2) Trace or oligo elements are primarily concerned with regulating the dynamic processes of enzymes; the line of demarcation between them and the first group is not clear. Minute amounts of these elements are needed to modify the kinetics of enzymic reactions. These processes are quite complex, and one element may play different roles in different enzyme systems. The elements are calcium, magnesium, iron, manganese, cobalt, copper, zinc, and molybdenum; having more than one function, the first three are common to groups 1 and 2. Typical concentrations in animal tissue are: Cu, 1 part in 10^7; Mo, 1 in 2×10^9; Co, 1 in 10^{10}.

3) Age elements include beryllium, aluminum, silicon, titanium, vanadium, chromium, nickel, arsenic, selenium, tin, lead, silver, cadmium, barium, gold, and mercury. Tissues as they age may accumulate many such elements, some with known physiological action, some with doubtful action, and some with no known physiological action. Civilization may expose man to some of these elements; some undoubtedly come from the soil. Some elements may be absent from tissue of stillborn babies; the concentration of such elements increases with age. Some elements with no known biological function are always found in tissues, often in a definite ratio, thereby suggesting that they may eventually be shown to be necessary for humans.

Some of the cumulative or age elements, notably nickel and chromium, may alter the reaction kinetics of enzymes, Furst continued. Indeed, excess or deficiency of any one of a number of elements can cause pathological changes or even death. In animals, excessive administration of some elements results in tumors. The following elements are claimed to be potential carcinogens: Al, Fe, Co, Cu, Zn, Se, Ag, Cd, Sn, Cr, Ni, As, Hg, and Pb. The last five have been definitely implicated as occupational hazards in industry. Many organic compounds also can cause cancer; they are usually classed as polycyclic hydrocarbons, azo dyes, aromatic amines, or miscellaneous.

Perhaps the most interesting feature of all these chemicals, Furst said, is that they have in the main, but not wholly, one chemical property in common: they or their metabolic derivatives can bind trace metals. Thus there is good empirical evidence supporting a hypothesis to the effect that trace elements, both essential and nonessential, play a vital role in cancer processes, and that carcinogenic compounds can conceivably act by chelation. Perhaps the most important feature of any theory or hypothesis of chelation in cancer is that it can be sustained or refuted by experiment. At least one clinically useful drug is now being tested as a result of this theory, Furst concluded.

A. H. Koffler (Ohio Northern University) showed how their interest in trace elements links geologists, geographers, and agriculturists on the one hand and pharmacologists and physicians on the other. Trace elements may provide evidence suggesting that certain unorthodox approaches to medicine and agriculture deserve more sympathetic appraisal than they are often accorded.

Recent advances in chemistry have led to the isolation of pure substances and of the so-called chief constituents of plants that are assumed to be responsible for their pharmacological action. But are these chief constituents really entirely responsible for the action? Nothing in a plant is a pure, isolated substance. These substances, be they vitamins, glycosides, or alkaloids, always occur with other nonpure materials: enzymes, coenzymes, trace elements. Much evidence suggests that some of the more potent medicinal effects are caused by the chief constituents plus something else, particularly one or more trace elements. It seems wise to investigate such synergistic effects.

In studies of 26 medicinal plants, their trace-element contents have been definitely related to those of the soils in which they were growing. The plants either are (or were formerly) listed in the *U.S. Pharmacopeia* or *National Formulary* or are well known in folklore. Some, usually classified as weeds, have very high contents of specific trace elements: for example, *Chelidonium maius* (greater celandine), *Cirsium arvense* (Canada thistle), *Melilotus* sp. (sweet clover), and *Phytolacca* sp. (poke root). Some of these weeds were and are highly regarded as medicinal plants. By reaching deeply, the roots of some can accumulate trace elements not found in shallow soils. When these plants die, Koffler went on, their trace elements enrich the upper layers of the soil. Thus some weeds may add value to a crop by enriching the soil in trace elements. In a plant community there are interrelations between plant and plant and between plants and the microflora connected with them.

Studies of these medicinal plants also bring out many points of nutritional significance. Trace-element relations vary widely among different genera and occasionally among different species, even when they are grown in a seemingly uniform soil. The trace-element content of different organs of a plant may vary widely; the reproductive organs generally tend to be richest. Trace-element content of vegetal matter may fluctuate widely during the growing season; in some instances it varies considerably during a day. Thus the witch doctor who collected specific plants for medicinal purposes on certain days of a particular season may have anticipated modern knowledge. Many cattlemen testify that specific plants poison their cattle at certain times of the year, while at other times they are harmless.

In spite of recent interest and work, Koffler continued, the roles of trace elements in plant, animal, and human nutrition are not yet precisely established. We have no clear picture of the complex interrelations existing between the many mineral elements found in plants, but it has been established that iron, copper, manganese, zinc, boron, silicon, and molybdenum are important to higher plants. We know that manganese is an important activator of enzymes that catalzye various stages of plant respiration, including glycolysis and the Krebs cycle. Recent work suggests that manganese takes part with enzymes in nitrogen metabolism. Carbonic anhydrase, which catalyses decomposition of carbonic acid to carbon dioxide and water, contains zinc. In some plants, B, Mn, Zn, Cu, Mo, and Co increase the rate of photosynthesis: in oats, Cu, Co, and Mo increase the stability of a complex of chlorophyll with lipoproteins.

Table 1. Trace elements (parts per million) in U.S. soils compared with worldwide averages (from Swaine, 1953); numbers of samples in parentheses.

Element	Maryland		New York	New Mexico		World-wide soils
	Garden (25)	Forest (12)	Garden (5)	Garden (12)	Natural soils (43)	
Fe	40,000	47,000	19,000	30,000	20,000	38,000
Mn	1200	1400	620	700	400	850
Ti	6000	5500	4000	5000	3500	4600
Cr	70	70	60	30	45	200
Ni	30	30	30	15	10	40
As	19	8	11	14	9	5
Pb	150	25	420	70	18	10
Cu	100	65	100	25	28	20
Zn	100	35	240	80	40	50

An infinite variety of physiological and morphological changes can be effected in plants by addition of trace elements either directly to the soil or by foliar spray. However, a slight change in the concentration of solutions may mean the difference between a beneficial and a toxic effect; indiscriminate spraying is dangerous, said Koffler.

Each day produces more and more evidence that ancient usages of plants for medicinal purposes were sound; plants seem to owe their healing properties to blends of ingredients in which trace elements may be important factors.

Helen Cannon (U.S. Geological Survey) said that agronomists have long known that soils vary greatly in their trace-element content. For years it has been an article of faith with agriculturists that the mineral contents of soils reflect to some extent the underlying rocks. Soils, in turn, to varying degrees project their trace-element contents into crops. This paper presented data (Table 1) collected in three areas —Washington County, Md.; Ontario County, N.Y.; and San Juan County, N.M.—shown by U.S. maps of mortality ratios to differ in rates of cancer and probably heart disease. Three important facts were made clear by Cannon's paper (Ann Fidler was coauthor). First, geology and geography can combine to produce soils and vegetal matter with widely differing contents of trace elements. Second, an excess of trace elements can be introduced into a food supply by a community that does not realize the significance of structural and sedimentary geology when establishing its water-supply and waste-disposal systems. Third, other kinds of pollution, for example, garden sprays and lead from automobile exhaust, can effect changes in the trace-element content of food. Available tables should be studied in detail. Table 1 includes only those trace elements whose values differ appreciably in both soils and plants.

Table 1 shows that Mn, Ti, Ni, and Fe vary from the normal by less than a factor of two. Chromium content is much lower and As, Pb, Cu, and Zn traces are much heavier in garden than in natural soils. Comparison of garden soils with natural soils provides a possible clue to the effects of contamination caused by man. Lead, zinc, and arsenic concentrations have probably increased in all three regions. The differences for arsenic are quite significant; those for copper are not conclusive.

Table 2. Trace-element contents (parts per million) of the ashes of some U.S. plants compared with those of average herbs; numbers of samples in parentheses.

Element	Maryland		New York	New Mexico		Average herbs*
	Garden produce (95)	Native vegetation (38)	Garden produce (19)	Garden produce (39)	Native vegetation (101)	
Fe	2700	3700	3000	765	6000	6800
Mn	370	3440	180	100	520	2100
Ti	280	390	530	85	1365	232
Cr	~10	~15	13	<10	30	14
Ni	<10	<20	<10	10	20	34
Pb	~30	~100	66	<10	20	41
Cu	90	150	90	50	65	120
Zn	500	300	500	350	460	630

* From the literature and from the U.S. Geological Survey (unpublished).

Vegetables growing in these garden soils are much poorer in trace elements than the native vegetation; and they are much more below average than are the soils in which they are grown. This discrepancy may be explained by the fact that the samples of vegetables were peeled. Data presented suggest that major concentrations of trace elements occur in the epidermal tissues. Cannon pointed out that in any study relating trace elements to human health it is important to prepare garden produce for analysis in the same manner as in preparation for human consumption. In the Maryland samples, the greater concentrations of zinc in garden produce than in native vegetation may reflect the galvanized roofing common in this area.

It is clear that Maryland and New York vegetables are higher in Fe, Mn, Ti, As, Cu, Pb, and Zn than are those of New Mexico. These differences may be attributed to geological differences in origin of the soil, topography, and hydrology of the regions, and artificial contamination in the gardens. Whether or not these variations can be linked with local mortality patterns has to be decided by competent medical authorities. Available epidemiological information certainly suggests some relations, Cannon concluded.

The last paper, by R. J. F. H. Pinsent (Birmingham, England; Research Committee of the College of General Practitioners), presented an entirely fresh and potentially important point of view. Pinsent suggested that general practitioners have a contribution to make in matters involving trace elements and epidemiology. Hospital and institutional science has tended to overshadow observational field research. Recent advances in medicine have led researchers away from the environment in which ill health begins and which may present discoverable causes.

The British College of General Practitioners plans to develop methods for minimizing observer error in the accumulation of data for analysis. To this end, diseases have been classified on the basis of the International Classification of Disease (I.C.D.). A central organization set up by the College coordinates research work. An early task was the National Morbidity Survey in 1955–1956, conducted jointly with the General Register Office in Britain; 170 doctors recorded every doctor-patient contact in 1 year. A vast amount of coding and punching produced the first accurate picture of the distribution pattern of illness in Britain; morbidity, rather than mortality, was examined. This success led to the development of simpler methods of recording and a plan for continued sampling by a smaller number of doctors. Various methods result in gathering of information about illnesses known to only the family doctor.

Variations and anomalies in the distribution of various diseases can be revealed and measured. Episode rates for sicknesses of all kinds can be related to geographical situation, socioeconomic factors, racial groups, sex, age, and other parameters in almost innumerable permutations. Comparison of morbidity patterns for different countries where social and geographical characteristics vary greatly answers some questions and gives leads for more specific studies.

Measurement of the distribution of illness in a community is even more valuable than the possibility of discovering relations between observed illnesses and causative factors in the environment in which the earliest phenomena are observed. The general practitioner is uniquely able to obtain accurate information on the immediate environment of his patients and their illnesses. His knowledge of peoples' homes, their habits of work and life, their physical and spiritual characteristics, their nutrition, and their exposures to special hazards is unique; and at least some of these features of environment can be reduced to measurable terms.

One special hazard that has concerned the College is imbalance in the trace-element content of the food and water supplies of a measurable community. A special study of an area known for some abnormal concentrations of metals is now going on in southwest England where the river Tamar separates Devonshire from Cornwall. Here an epidemiological study (by E. D. Allen-Price) of the distribution of cancer deaths had suggested that high mineralization was a possible factor behind an unusual cancer-mortality pattern in the area. The College study is wider, covering the whole range of illnesses seen by the general practitioner. Work on vegetables, stream sediments, and water supports both Allen-Price's conclusions and the activities of the College; further geochemical investigations are under way. Devonshire and Cornwall are sites of important mineralization; many metals

have been mined there for centuries, including copper, tin, lead, zinc, arsenic, and silver, all of which occur in unusually large amounts in vegetables grown in the area.

Meanwhile, Pinsent continued, other studies of areas known for less abnormal amounts of trace elements are being carried out. It is hoped that these studies will provide useful leads for more detailed investigations.

Family doctors must depend to some extent on other scientists, veterinarians and botanists, who may be able to provide complementary evidence of mineral imbalances deduced from animal and plant diseases in the area. The general practitioner has contacts with all other disciplines within medicine, and this research puts him in touch with colleagues in almost every branch of natural science. Only by interdisciplinary cooperation can investigations of trace elements be carried out effectively, said Pinsent.

The College is anxious to see comparable studies carried out in other lands, particularly in those in which minerals are deficient rather than in excess. Morbidity-recording methods developed in England are already employed in Australia and New Zealand, and wider use in Canada is hoped for. However, recording ledgers can be used anywhere by general practitioners without modification.

The College of General Practitioners also uses another approach. Its research department uses various notification techniques to discover the whereabouts of clusters of reported cases of a given disease. Family physicians notify their central unit, and these reports are plotted. At present, leukemia and multiple sclerosis are being reported, and new clusters of the latter have been discovered. The next step will be to study geochemical and other features of these localities in search of common factors. Pinsent concluded as follows:

"I have spoken of the work, and of the plans and hopes of a number of amateur research workers in family practice in Britain. We have no achievements to display, no great discoveries to record. We are convinced, however, that with the help of our colleagues in the other sciences, we can add a new dimension to research into the beginnings of disease."

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