Trace Elements: A Growing Appreciation of Their Effects on Man

Scientists have for some time recognized that trace concentrations of certain elements, such as iron and zinc, are essential to human metabolism; that other elements, such as lead and cadmium, are toxic at similar concentrations; and that still others, such as selenium, can be both beneficial and toxic within a fairly narrow range of concentrations. Only very recently, however, have most scientists begun to appreciate the full extent and the great complexity of the interactions between environmental trace elements and human health.

New research is continually expanding the number of metabolic systems known to be affected by trace elements and is revealing many hitherto unsuspected relationships between trace element concentrations and abnormal states of health. The time may thus be fast approaching when evaluation of trace element concentrations will play a fundamental role in the diagnosis of illness and when manipulation of those concentrations may play an even greater role in its prevention.

The detrimental effects of certain trace elements and their derivatives have become very well known in recent years. Lead and methylmercury, for example, have been shown to damage the central nervous system; the severity of such damage is amply demonstrated in a report by F. Bakir and Thomas W. Clarkson and their associates at the University of Baghdad and the University of Rochester, respectively, of a recent episode of methylmercury poisoning in Iraq (page 230). Beryllium is highly carcinogenic, and is also both a short-term poison in high concentrations and a long-term systemic poison in low concentrations. Nickel carbonyl's have been implicated as a source of lung cancer, and cadmium, arsenic, selenium, and yttrium have all been shown to be carcinogenic in laboratory animals.

Many trace elements are, of course, beneficial. At the latest count, 14 different trace elements have been identified as essential to human health. Cobalt, zinc, and manganese, for example, serve as cofactors for various metabolic enzymes, and iron is an integral component of hemoglobin. Trace concentrations of fluoride in water have undeniably assisted in the prevention of dental caries, although some scientists still argue that it may be harmful to other human systems.

Some investigators, such as Raymond J. Shamberger of the Cleveland Clinic Foundation, Cleveland, Ohio, suggest that trace concentrations of selenium and vitamin E in breakfast cereals are responsible for the nearly 70 percent decline in the incidence of gastric cancer in the United States and Canada since the 1930's. And a growing body of statistical evidence, compiled in large part by H. A. Schroeder of Dartmouth Medical School, Hanover, New Hampshire, indicates that the incidence of cardiovascular disease is substantially lower in areas where the municipal water supply contains high concentrations of dissolved minerals.

Subtle, Poorly Defined Interactions

These examples represent only a few of the most obvious interactions of trace elements and human physiology. Many such interactions are far more subtle or much less well defined, however, and the majority are probably still unknown. Their scope and diversity can perhaps best be illustrated by considering some of the results reported last month at the University of Missouri's seventh annual conference on Trace Substances in Environmental Health. This interdisciplinary meeting, cosponsored by the university's Environmental Trace Substances Center and the National Science Foundation, provides examples from many different areas of research.

The complexity of monitoring the large number of trace elements that may participate in human metabolism was suggested by Fred Losee of the Eastman Dental Center in Rochester, New York. Examining samples of teeth of individuals from widely separated areas of the United States, Losee concluded that no less than 43 elements are incorporated as regular constituents of developing human dental enamel. Another 25 elements were also detected in some samples, and 30 elements—primarily the heaviest ones—were not detected at all. Any complete analysis of trace elements in teeth, and presumably in other body tissues, would thus entail detection of a very large number of elements.

Most of the elements in teeth probably have no effect on the formation of dental caries, but in recent years it has been suggested that molybdenum, vanadium, boron, strontium, barium, lithium, titanium, and aluminum may help prevent caries, and that lead, copper, zinc, and chromium may increase caries. These contentions, argues D. M. Hadjimarkos of the University of Oregon Dental School, Portland, are based on the erroneous assumption that drinking water is the primary source of trace element ingestion in man. In fact, he says, it has been well established that, with the exception of fluoride, food is the main source.

Nonetheless, three independent epidemiological studies indicate that selenium, at least, is capable of increasing caries when consumed during the period of tooth development. Experiments with rats and monkeys, Hadjimarkos says, indicate that selenium ingested during tooth development is incorporated into the protein components of enamel. This incorporation inhibits mineralization of the tooth, and thus makes it more susceptible to decay.

Incorporation of molybdenum into the enamel, in contrast, tends to stabilize the structure of the tooth, according to Clive C. Solomons of the University of Colorado Medical School, Denver. Experiments with rats, he says, show that this stabilization is consistent with previous reports of molybdenum-mediated resistance to caries. A different effect is observed in bones, however. Solomons' experiments show that there is a significantly reduced uptake of calcium by the bones of molybdenum-treated rats, and that the rats thus suffer from osteoporosis, a weakening of the bones' macrostructure.

Cadmium has an even more pronounced effect on bones, according to Jun Kobayashi of Okayama University, Kurashiki, Japan. Kobayashi had previously established a relationship between the mysterious syndrome called itai-itai ("ouch ouch") disease that affected residents of Japan's Jinzu River basin in the late 1950's and the discharge of cadmium into the river by a large factory. Ingestion of cadmium by the residents, he suggested, led to the severe and painful decalcification of skeletal bones and multiple pathological fractures characteristic of the syndrome. Recent experiments with rats have substantiated this thesis, he says, and, in August of last year, Japanese courts accepted its validity and awarded compensation to the affected residents.

Many other instances of poisoning by natural or man-made sources of trace metals will undoubtedly be discovered as scientists extend their investigations of mysterious illnesses. One unusual example was reported by J. Hartmans of the National Council for Agricultural Research, Wageningen, the Netherlands. He found that several unexplained deaths of sheep in the Netherlands resulted from grazing them directly beneath high-voltage copper power lines in industrialized areas. Examination of the soil directly beneath these lines showed that its copper content was frequently more than twice that of soil from locations only 100 meters windward of the lines.

The concentrations of copper were not high on an absolute scale—rarely more than 50 parts per million (ppm) —but they were high enough to affect sheep, which are more susceptible to copper poisoning than other domestic animals are. Because similar copper enrichment of the soil under power lines was not found in rural areas, Hartmans suggests that erosion of copper from the cables may result from the action of sulfur dioxide in polluted air.

Natural sources of trace elements may also produce unexpected effects on health. Maurice L. Sievers of the Phoenix Indian Medical Center, Phoenix, Arizona, suggests that Pima Indians of the Gila River Reservation in Arizona may provide a textbook example of these effects. Among Pimas who have spent most of their lives on the reservation, the incidences of obesity, cholesterol gallstones, cirrhosis of the liver, and diabetes mellitus (45 percent of adult Pimas are diabetic) are substantially higher than in the population at large, and the incidences of duodenal ulcer, hypertension, atherosclerosis, and cancer of the lung and breast are substantially lower. At least some of the effects, Sievers contends, may result from environmental trace elements.

Domestic water on the reservation is unusually enriched in several elements, including sodium, chlorine, calcium, magnesium, sulfate, strontium, boron, lithium, and molybdenum, and is deficient in the required elements copper, zinc, and manganese. Certain food plants on the reservation also tend to concentrate particular elements. Mesquite beans, for example, accumulate strontium; cabbages accumulate sulfate; beans concentrate molybdenum; wolfberries (used for jelly) contain an extraordinary amount of lithium, 1120 ppm. Initial hypotheses being investigated by Sievers are that the hardness of the reservation water may be responsible for the decreased prevalence of atherosclerosis and hypertension among the Pimas, and that the high lithium content of the water and plants may be linked to the low frequency of atherosclerosis and myocardial infarctions. Other geochemical correlations may be developed, he believes, as the investigators obtain greater knowledge about trace element concentrations in various organs of the Indians.

Interference with Other Elements

Concentration of various elements are closely interconnected in human physiology, and there is growing evidence that at least some effects of toxic trace elements result not so much from inherent toxicity of the elements as from their interference with the function of other elements. N. F. Suttle of the Moredun Research Institute, Edinburgh, Scotland, reported, for instance, that molybdenum interferes with the copper metabolism of several species of ruminants when it is administered in concentrations frequently found (5 ppm) in natural foodstuffs. The molybdenum apparently acts by inhibiting the absorption of copper from dietary sources, and could thus produce symptoms of copper deficiency.

Robert E. Burch of the Veterans Administration Hospital in Omaha, Nebraska, found that the addition of 10 ppm of selenium to a rat diet low in protein hindered the growth of the rats, produced enlargements of their hearts and livers, and lowered the concentrations of magnesium, copper, and especially manganese in these and other organs. The effects were magnified when the selenium was supplemented with cobalt (10 ppm). These symptoms, Burch says, are similar to those observed in the syndrome of "beer drinker's cardiomyopathy" that produced many deaths in Omaha, Minneapolis, and at least two foreign cities in 1965 and 1966. The syndrome had previously been attributed to the toxicity of small amounts of cobalt added to commercial beer to stabilize its foam, but Burch now theorizes that the cobalt may have potentiated the toxicity of naturally occurring selenium in the affected cities.

Despite the growing body of knowledge about trace elements and their association with illness, there has been little application of research findings to clinical medicine, contends Ross H. Seasly of the Kettering Medical Center in Kettering, Ohio. This conclusion is exemplified, he says, by the fact that during the last 10 years, Kettering's clinical laboratory has never received a request for analysis of trace metal concentrations in a patient. Yet there is mounting evidence that such an analysis can be quite useful in diagnosis.

Arthur Flynn of the Case Western Reserve University School of Medicine, Cleveland, Ohio, has found that stresses such as operations, trauma, and burns produce an elevation in the concentration of zinc in the patient's blood. This elevation is proportional to the severity of the stress, and disappears when the stress is abated. He thus suggests that analysis of zinc concentrations in the blood would provide one method of monitoring the recovery of critically injured patients.

In a paper prepared for the conference but not presented, M. D. L. R. Nosdrjukina of the Institute for Geochemistry and Analytical Chemistry of the Academy of Sciences of the U.S.S.R., Moscow, reports that the concentrations of trace elements in the blood may be useful for diagnosing certain types of heart disease. He finds, for example, that blood manganese and nickel concentrations rise sharply just before the onset of myocardial infarctions (death of heart muscle caused by lack of blood), and that these changes may be used as diagnostic criteria at an early stage of the disease. Similar correlations have been observed for other types of heart problems. He also reports that certain medicinal herbs containing high concentrations of trace elements are very useful in the complex therapy of some types of heart disease.

Clearly, then, there is a great deal yet to be learned about the effects of trace elements on human physiology and a great many benefits to be obtained from this knowledge. Equally clear, however, is the realization that much of the research on trace metals may be to little avail if there is not a narrowing of the gap between research results and clinical applications and an increased effort to place this new knowledge in the hands of practicing physicians.—Thomas H. Maugh II