5-1-1972

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Henry A. Schroeder

Dan K. Darrow

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RELATION OF TRACE METALS
TO HUMAN HEALTH

By Henry A. Schroeder and Dan K. Darrow *

INTRODUCTION

For the past 150 years, as the result of increased industrial activity, civilized man has been exposed more and more widely to metallic contaminants in his environment. For example, the canning of foods, with its attendant dangers, was introduced in the Napoleonic Wars and became wide-spread after the American Civil War. The smelting of ores and the refining of metals also have long histories and were responsible for the introduction of many metals into air and water. Although in earlier times, human exposures in this regard were usually local, during the past 50 years they have become fairly general. Exposures to lead have occurred in circumscribed areas of the world for 3000 years or more, and were especially high among the Roman upper classes; moreover, in previous centuries, the use of lead pipes in soft water areas sporadically caused lead poisoning in persons drinking such waters. It was not, however, until 1924, when alkyl lead was put into gasoline as an anti-knock agent, that whole civilized populations were exposed to lead at an annually increasing rate. Cadmium was an industrial curiosity in 1900, but today its use is sharply increasing in an exponential curve, with resultant contamination of air, water, and food. Mercury was widely used for amalgamation of gold from crushed ore, but it was only later discovered to have catalytic and fungicidal properties, which in the forms of treated waste seeds and effluents, caused considerable contamination of the stagnant lakes into which they were discarded. Antimony was used as a cosmetic by past Cretan women, but today it is everywhere in glazes, enamels, and type metal. Almost every civilized person is exposed to silver, gold, vanadium, chromium, titanium, nickel, germanium, arsenic, sele-

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nium, tellurium, niobium, zirconium, barium, in amounts exceed-
ing those to which his forebears were exposed, and those to which
wild mammals are exposed today.

The earth is rapidly becoming a place where few human beings
can be found to exist at background environmental levels. As a
result, the body burden of many elements on present-day man is
considerably greater than that which existed with respect to prim-
itive man. The question naturally arises: has the recondite toxicity
of any of these elemental substances become evident in metabolic
breakdown causing disease or in slow metabolic deterioration caus-
ing decreased longevity?

Suspicion falls on any element which accumulates in aging human
tissues. Of the trace elements essential to life, health, and optimal
function—vanadium, chromium, manganese, iron, cobalt, copper,
possibly nickel, zinc, selenium, strontium, molybdenum, fluorine,
iodine—none accumulate under present exposures, except in un-
usual and individual situations where homeostatic mechanisms for
repulsion of excesses and conservation of deficiencies are genetically
disturbed, or when exposures are extremely large. Copper-and iron-
storage diseases occur in man as genetic traits.

The non-essential trace elements found in appreciable concen-
trations in the environment can be divided into those with high
natural levels in the earth's crust—silicon, aluminum, titanium,
barium, zirconium, niobium, lithium, lanthanum, gallium—and
those with low natural levels but with high potential for industrial
contamination. Since mammals developed in the presence of high
environmental concentrations of the first group, one can assume
that they had low orders of toxicity; the validity of this assumption
can be supported by experimental evidence.

Elements found in low concentrations on the earth's crust but
mined and used industrially in large quantities are tin, germanium,
beryllium, arsenic, molybdenum, mercury, antimony, bismuth, cad-
mium, silver, selenium, gold, tellurium. As these elements also
occur in low concentrations in sea water, life developed and mam-
mals evolved without the need of elaborate mechanisms for hand-
ling them. Therefore, today, when environmental exposures in-
crease manyfold, some of them accumulate in human tissues and
exert recondite toxicity. The balance between absorption and ex-
cretion is disturbed.

All substances are toxic in large enough amounts, that is, when

homeostatic mechanisms for excretion are overcome. In fact, water is one of the most toxic substances known, when one compares the normal intake to the toxic intake. A man can drink 3 liters a day, but if he drinks 9 or 10 liters, his kidneys may fail. A person can eat 10 to 15 grams of sodium chloride a day without adverse effects, but if he eats 40 grams he becomes edematous. The difference between the normal intake of a trace element by food, water, and air and the toxic intake depends upon the efficiency of homeostatic mechanisms for excretion, but except for a few instances, is several orders of magnitude higher.

A rough idea of present day exposures to the products of industrial metals can be found by analyzing approximate annual U.S. industrial consumptions in terms of the elements necessary for life, those with known toxicities, those slightly toxic and those inert.[1] Of the 16 essential metals, present exposures offer no hazard whatsoever. High exposures in a few local or isolated instances can cause manganism in miners, lung cancer in chromate workers, nickel-carbonyl cancers in nickel workers, or bony abnormalities from high fluoride wells and selenium poisoning (a non-fatal ailment) in persons in seleniferous areas. Yet, although many human exposures have increased to levels potentially of concern, other human exposures have decreased, as a consequence of modern food practices in refining and processing our caloric energy.

In order to ascertain recondite toxicity, it is necessary to duplicate in small mammals the experiments modern man is now unwittingly performing on himself during his life-time.[2] Therefore, we constructed a laboratory of wood, covered with plastic varnish, on a remote Vermont hill-top and designed it so as to exclude contaminating metals from air and water. Large numbers of rats and mice were exposed to single elements in low doses for a life-time. Recondite toxicity was evaluated in terms of growth, life span, longevity, changes in serum, tumors, microscopic pathology, disease, and tissue content of the element fed. Reproduction of exposed animals was also evaluated.

Under these life-time exposures, 30 elements were given to mice and 20 to rats in drinking water. Little or no subtle toxicity was shown by hexavalent chromium, fluoride, molybdenum, vanadium, nickel, arsenic, barium, aluminum, titanium, zirconium, or niobium. Although carcinogenesis was exhibited by selenate, rhodium, and palladium, human exposures to these elements are very low.

EXPERIMENT RESULTS

Six toxic metals will be considered separately below, as each one presents its own problems. Brief mention will also be made of slightly toxic metals and of elements that are probably inert.

Lead

Lead is the largest contaminant of the environment. About one kilogram per day per capita is discharged from the tail pipes of automobiles, to enter air, water, and soil.[3] Human intakes from urban air are about equal to absorptions from food. Lead accumulates in human bone and other tissues with age. No lead has been found in children's bones, nor in the bones of Peruvian Indians circa 1200 A.D., and only little lead has been found in monk's bones up to 300 A.D. The body burden of Reference Man today is 121 mg with a range of 9 to 480 mg. It is probable that today's burden is 100 times that of primitive man. The margin between "normal" blood levels and levels considered to be toxic is becoming increasingly narrow.[4] At all levels of urban exposure, there is interference with erythrocyte delta-aminolevulinic acid dehydrase, a red blood cell enzyme, in proportion to blood level.[5]

Overt lead poisoning from children eating lead paint is well known, with symptoms ranging from mental retardation to convulsions and coma. Air borne lead from motor vehicle exhausts has been suspected to add to intakes of urban children playing at street level, thereby causing poor performance in school. Subclinical lead toxicity in urban dwellers has been also suspected but not yet delineated. There is enough lead (200 ppm) in the grass growing along a secondary highway in our town to abort a cow; lead polluted hay killed a horse in Wales and 13 horses in California.[6]

In rats and mice exposed to lead in water, there was early mortality, shortened life span, and susceptibility to infections. Old rats lost excessive weight. When chromium was added to the water, however, effects on mortality and life span were largely prevented. Lead that was given to rats caused focal myocardial fibrosis in a quarter of such animals.

The cause of this rapid build-up of environmental lead is the addition, since 1924, of alkyl lead to gasoline for use as an antiknock agent; this lead has now contaminated the Northern Hemisphere.[7] One can predict with reasonable accuracy that subtle lead

poisoning under the guise of several vague symptoms will soon appear in urban populations. The prevention of this disease is the elimination of alkyl lead from gasoline, and, to a minor extent, the abatement of lead fumes from smelters and refineries. Once the disease has occurred, the cure will be difficult and slow.

Cadmium

An insidious toxin, cadmium is a recent addition to the growing list of environmental contaminants added to low background levels. In nature, it is always associated with zinc, at an approximate ratio of 1:500. It has the ability to displace zinc in biological systems and to interfere with zinc's function in enzymes.

In rats fed low doses of cadmium for life, the metal accumulates in blood vessels, kidney, and liver; and, with its accumulation, there is also an accumulation of zinc. High blood pressure appears in increasing frequency after about a year, and is universal after 30 months of age.[8] Associated with hypertension are the typical scleroses of the renal arterioles, enlargement of the heart, and sclerosis of coronary and other blood vessels.[9] The degree of arteriosclerosis in the aorta is enhanced.[10] The findings in the rat reproduce the clinical and pathological picture of human hypertension.

The cadmium in rat and human kidney and liver is bound partly in metallothionein, a zinc and cadmium protein. In blood vessels, it is probably bound to sulfydryl groups. Most sulfur-containing chelating agents, such as gluthathione, have a higher affinity for cadmium than for zinc. The contrary is true for most oxygen nitrogen ligands.

There are, however, a few chelating agents not containing sulfur and having somewhat higher stability constants for cadmium than for zinc. We chose one such agent, with high constants for both metals, on the basis that cadmium is tightly bound in tissues (gluthione, for example, may not bind them as well as tissues do). The zinc-sodium complex of cyclohexane diamino tetraacetic acid (CDTA), when injected into rats, reduced the blood pressure to normal and exchanged some renal and hepatic cadmium for zinc. Blood pressures remained normal for many months.[11]

Injected cadmium also produced hypertension, relieved by the zinc chelate.[12] These observations have been confirmed in rats by Perry and Erlanger,[13] who fed cadmium to the animals and found resultant hypertension, and by Thind et al., who injected cadmium

into rabbits and dogs.[14] Vascular reactivity was altered by cadmium, and was restored by the zinc chelate.[15]

In respect to human hypertension, Perry and the author Schroeder found much greater amounts of cadmium in the urines of patients with hypertension than in normotensive urines.[16] The death rate from hypertensive heart disease is highly correlated with the concentration of cadmium in air[17] and milk.[18] People dying of hypertension had more cadmium in their kidneys and a higher ratio of cadmium to zinc than did people dying of accidents, coronary heart disease, cancer or miscellaneous causes from around the world.[19] The prevalence of hypertension in hospital admissions was correlated with renal cadmium in various geographical areas of the world.[20] Thind et al. found higher serum levels of cadmium in hypertensives than in normotensives.[21] Not supporting this hypothesis, however, are Morgan's findings of no differences in renal cadmium or zinc in a group of Negroes with or without hypertension.[22] Methodological differences may or may not account for these findings.

There is a curious paradox in the relation of cadmium to hypertension. Swedish cadmium workers, who are exposed to dusts and who accumulate amounts large enough to induce proteinuria and renal damage do not become hypertensive in excess. Likewise, persons who are exposed to large amounts in Japan and who have resultant decalcification of bone (itai-itai disease) do not have excess incidences of hypertension. Apparently low exposures induce hypertension, while high exposures do not. When enough cadmium is accumulated to produce toxicity, hypertension is not especially common, whereas less than this amount induces hypertension. This phenomenon is unexplained.

In rats made hypertensive by partial constriction of a renal artery, the feeding of cadmium enhances the hypertension. When the operation fails to cause hypertension, the feeding of cadmium induces it.[23] Thus, there is synergism between the two methods.

Cadmium in air appears to come mostly from industrial sources, not from the burning of fossil fuels. Cadmium has been linked to pulmonary emphysema. Higher values have been found in the liver and kidney of patients with emphysema and with lung cancer than in those of the controls.[24] Exposed workers also can suffer from emphysema.[25]

An isolated area of Japan was irrigated by waters of the Jintsu River, into which a zinc mine and smelter was pouring its effluents

for many years. Grains and fish were contaminated by cadmium and lead. Persons living on those foods eventually exhibited severe softening of their bones, with many fractures, deformities, and much pain ("ouch-ouch" disease). Their bodies contained large amounts of cadmium and lead.[26] However, no other examples of this disorder have been reported. The disorder was probably the result of low levels of calcium in the diet plus high quantities of lead and cadmium. This disease represents an extreme example of multiple toxicity.

Nickel

Although nickel dusts can cause lung and nasal cancers in exposed workers[27] and although nickel metal can cause eczema,[28] at present exposures in air and water, nickel offers little or no hazard to the general population. When finely divided nickel is exposed to hot carbon monoxide, as might occur during the incomplete combustion of coal and petroleum (which contain nickel) the carbonyl can be formed. Cigarette smoke, for example, contains nickel carbonyl. Although this compound is carcinogenic to rats and man,[29] life-time exposures of rats and mice to nickel acetate did not cause excess tumors or any other effect.

Antimony

Rats and mice exposed to antimony in water had shortened life spans.[30] In large doses, it will produce heart disease. Present exposures are probably low, but this metal is a potential hazard.

Beryllium

Air borne beryllium can cause beryllosis in exposed workers, and even in the families living near beryllium smelters and refineries.[31] It is a serious, chronic lung disease. Beryllium can cause cancer in rats. Although general exposures are low, this metal ranks high in toxicity.

Mercury

There appears to be no hazard to the general population from inorganic mercury or aryl mercury compounds. Mercury is ubiquitous on this planet,[32] and is found in every living thing. Fish concentrate mercury and accumulate it with age, and fish eaters,

be they fish, flesh or fowl, have more mercury than non-fish eaters. This age-accumulated mercury is obviously non-toxic; for if it were toxic, fish eaters would suffer from mercury poisoning, and seals, otters, porpoises, and other mammals, including man, that live on fish would not survive.

Alkyl mercury, however, is another matter. Alkylation of lead, tin, and mercury converts mildly to moderately toxic substances into compounds with high toxicity. There have been two out-breaks of methyl mercury poisoning—in Minimata and Niigata, Japan—resulting from the dumping of methyl mercury catalysts by plastic plants into a bay and a river. This compound was taken up by fish and shellfish, and it poisoned 121 people in Minimata and 47 in Niigata, with 52 dead.[33] When the dumping of methyl mer-cury was stopped, the epidemics ceased, and no one else in Japan was affected.

Alkyl mercury has been widely used as a fungicide on seed grains. When people disregarded the labels and ate treated wheat or other grains, they were poisoned by methyl or ethyl mercury. Such out-breaks have occurred from time to time in Iraq, India, and Guate-mala, with many deaths. The most recent case was in Alamogordo, New Mexico, where a hog that had been fed treated wheat was eaten by members of a farmer's family, three of whom consequently suffered permanent injuries.[34] These poisonings from methyl mer-cury, however, have little to do with the present scare regarding mercury accumulation in fish. It must be recognized that mercury has always so accumulated.

Using the method of Westoo, analyses of fish, meat, eggs and poultry have shown that about 90 percent of the mercury is in the form of methyl mercury.[35] This appears true for both fresh water and marine fish. On the one hand, either the method of digestion or the method of analysis gives falsely high values of methyl mer-cury, or, on the other hand, methyl mercury in tissues is so tightly coordinated to sulfur and protein as not to be toxic.

Man has not polluted the oceans with mercury. If the world's annual consumption of mercury of some 10,000 tons were poured into the ocean, only 3 tons would not precipitate to the bottom, and this amount would be dissolved in 1.42 quintillion tons of sea water. The mercury in marine fish is thus background mercury. And that in fresh water fish is background mercury plus industrial mercury dumped in fairly stagnant lakes; in this case, fish take up extra mercury from the food chain.

As a final point, it may be noted that mercury in air comes largely from the burning of fossil fuels.

Slightly Toxic Metals

There are nine metals exhibiting slight or low grade toxicity to some forms of life. All of them occur on the earth's crust in low concentrations, less than 3 ppm, and in the body of man in less than 18 mg amounts. Tin and arsenic are the two most highly consumed.

The toxicity of tin to mammals is low. Fed to mice and rats for life, it did not affect life-span or longevity of males, but lessened longevity significantly in female rats. Tin accumulated in spleen but not in other organs appreciably.[36] No disorders dependent on tin are known in man.

Arsenic also had a low order of toxicity to rats, as it did not affect growth, life span or longevity.[37] It accumulated to high concentrations in all tissues, especially aorta and red blood cells. In mice, however, arsenic depressed life spans and longevity significantly, and it accumulated in mouse tissues to a lesser extent than it did in rat tissues.[38] In man, chronic arsenic toxicity is accompanied by skin lesions which become cancerous. There was an epidemic of arsenic toxicity and skin cancers in Taiwan from naturally contaminated well-water several years ago; similarly, a child in Fallon, Nevada, was also poisoned by arsenic in a well.

As for other slightly toxic metals, in preliminary experiments tungsten given to rats produced high blood sugars, probably as a metabolic antagonist to molybdenum and chromium. Germanium fed to mice shortened life-spans and longevities of males, accumulated in tissues, especially the spleen, and suppressed the formation of tumors.[39] In rats, it caused fatty degeneration of the liver, shortened life spans and suppression of tumors, and accumulated in tissues to some extent.[40] Palladium and rhodium were somewhat carcinogenic in mice.[41] Tellurium shortened life spans of female mice,[42] but not of rats.[43] Human exposures to these elements are low.

Elements Probably Inert

There are eight elements that are relatively inert as to biological processes. Six of them are abundant on the earth's crust and in man's body, and five are consumed industrially in fair sized quanti-

ties. Aluminum, barium, and titanium accumulate in human lungs with age, probably from natural dusts. Most of the barium used industrially goes into muds for oil-well drilling. Human exposures to these elements are wide-spread, and toxicity, except to certain compounds in large concentrations, are rare. They can be neglected at present levels as hazards to health.

DEFICIENCIES OF ESSENTIAL TRACE ELEMENTS

Primary or secondary deficiencies of the bulk elements are well known and need not be considered here. What are less well understood are deficiencies of the essential trace metals in human health. Although homeostatic mechanisms are efficient in most cases, deficiencies can occur from depletion of foods by refinement—such as flour, sugar and fats or oils—and by marginal diets therefrom. We can discern two deficiencies common in human beings in this country, which deficiencies may have adverse effects on health, and we can suspect others from analytical data on human tissues compared to data on other mammals.

Zinc

Low plasma levels of zinc have been described in a variety of conditions and diseases;[44] they may be secondary to whatever is the disease in question. Slow healing of wounds, especially of indolent ischemic ulcers of the lower extremities, has been reversed by oral zinc supplements, often with dramatic results.[45] Open operative wounds in young airmen have shown rapid healing with oral zinc.[46]

Circulation in ischemic extremities has improved with oral zinc supplementation, so as to relieve intermittent claudication.[47] Yet low blood pressure in these extremities has not improved, suggesting that zinc acts to dilate arteries beyond an organic constriction. Even early gangrene has healed under zinc supplements. These observations suggest that marginal zinc deficiency may affect these conditions, and that restoration of plasma zinc to normal helps to correct them.

Chromium

Atherosclerosis is in varying degrees a disease common to all and is conditioned by dietary factors. Biochemically it is characterized by elevated serum cholesterol levels and by diminished tolerance to glucose; anatomically it is characterized by plaques in the major

arteries—aorta, heart, brain, or legs. Rats raised on low chromium intakes show glucose intolerance, elevated serum cholesterol levels, and plaques in their aortas.[48] These changes are duplicated when refined sugar is the major source of calories. They are prevented by feeding the subject chromium in water, or by feeding it dark brown sugar, which is fairly high in chromium.

The human body burden of chromium is low in Americans and high in non-Americans; moreover, in the former, it declines with age. At various ages, from 10 to 25 percent of subjects are deficient. Persons dying of coronary heart disease had virtually no aortic chromium, whereas normal amounts appeared in those dying of other diseases.[49] In some persons, oral chromium complexes have lowered serum cholesterol and have improved glucose tolerance, but the effects are not consistent.

Other Essential Trace Metals

School lunches have been found deficient or marginal in chromium, copper, and manganese.[50] Man contains much less manganese than do wild mammals, yet domestic animals raised for profit are fed 20–30 times the amounts that appear in human diets. The reasons for this discrepancy have not been explained.

CARCINOGENICITY OF TRACE METALS

Many metals are directly carcinogenic when injected into animals, and they usually produce sarcomata. By the oral route, however, only four produce tumors: lead (at 0.1–1.0% lead acetate in feed), selenium (at 3 ppm in water), and rhodium and palladium (at 5 ppm in water). In man, arsenic in large doses can lead to skin cancer. By inhalation, three metals—beryllium, hexavalent chromium, and nickel—produce lung cancers in animals, and the two last mentioned metals cause cancer in heavily exposed workers. Present levels in food, water, and air appear to offer no hazard to the population at large, except in certain instances of high concentrations. We cannot exclude, however, the possible effects of nickel carbonyl resulting from the incomplete combustion of coal, petroleum, and gasoline with nickel additives.

SUMMARY AND CONCLUSIONS

The effects of various trace elements on human health have been reviewed in the light of annual industrial consumptions, natural

abundances (on the earth's crust, in sea water, and in the contents of Reference Man) and changes in experimental animals fed low doses for life.

Fourteen metals and two non-metals are essential for life or health of mammals. All but two are mined in large amounts, are abundant on the earth's crust, and are found in human tissues in sizeable quantities. Most of these metals are non-toxic to mammals in ordinary concentrations. Five metals occur in low abundances, are consumed industrially in sizeable amounts, occur in the body of man, and are toxic of themselves. Of these, lead and cadmium are prevalent in man. Nine metals have low orders of toxicity and occur at low crustal abundances. Eight have little or no toxicity, of which six are abundant.

Metals in the environment of potential hazard to man are lead, by far the largest pollutant, cadmium, which may influence hypertension and emphysema, nickel as the carbonyl which is carcinogenic, antimony which is toxic, beryllium which can cause berylliosis, and methyl mercury which is highly toxic. At present levels of exposure, lead, cadmium, and possibly nickel are potentially hazardous to health. Only under special circumstances and in special compounds are a few other elements hazardous.

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FOOTNOTES

* Dr. Schroeder is Professor Emeritus, Department of Physiology, Dartmouth Medical School; Mr. Darrow is Staff Assistant, Department of Physiology, Trace Element Laboratory, Brattleboro, Vermont. This article has been preprinted with the permission of Plenum Press, which will publish the article in *Chemical Analysis of the Environment*, a volume in PROGRESS IN ANALYTICAL CHEMISTRY, 1972.

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