SPECIAL ARTICLE

Cadmium, Chromium, and Cardiovascular Disease

By Henry A. Schroeder, M.D.

SUMMARY
Observations made in the last 15 years by the author and others concerning the effect of trace metals, particularly cadmium and chromium, on animals and man are reviewed with special reference to hypertension and atherosclerosis. These trace metals come from the soil or sea. Among the topics covered are cadmium hypertension in rats, diabetes mellitus and chromium deficiency, deficiency sources, and possible losses of chromium, and the influence of drinking water on death rates from atherosclerosis. The conclusions are that one common form of hypertension is probably an example of accumulation of cadmium in the kidney and that deficiency of chromium may influence glucose and lipid metabolism and affect atherosclerosis. Other trace elements may contribute also.

Additional Indexing Words: Atherosclerosis, Diabetes mellitus, Trace metals in wheat and flour, Renal cadmium and zinc

This presentation, the twenty-seventh lecture of a series honoring the memory of George E. Brown, gives me the opportunity to assemble a number of observations made during the past 15 years on certain elemental factors which I believe are involved in the pathogenesis of two common vascular disorders. Dr. Brown was interested in peripheral vascular diseases. In their broadest terms, both arterial hypertension and atherosclerosis can be considered diseases of the peripheral blood vessels. My discussion will be confined to these two conditions, and to the relation of two trace metals to their presence in animals and man.

Progress in science is often the result of chance observations. In 1949, Reubi found that 1-hydrazinophthalazine (hydralazine) had the unique property of increasing renal blood flow of human hypertensive patients in the face of a lowered blood pressure. This compound, which had a prolonged hypotensive effect in renal hypertensive dogs, was stored in metal-capped bottles. Perry noticed that the solution was corroding the caps, despite a neutral pH. He tested the compound against various metal ions and found that it chelated a number of them. Five other drugs more or less effective in human hypertension also had the property of binding some of the...
trace metals present in the human body: thiocyanate, nitroprusside, azide, 2-3 dimercaptopropanol (BAL), and ethylene diamine tetraacetic acid (EDTA). None of these agents appeared to act on the sympathetic nervous system. Hydralazine binds zinc, iron, and cobalt as well as vanadium, chromium, manganese, and copper.

Small doses of known chelating agents with nitrogen, sulfur, oxygen, and carbon ligands, or donor atoms, which bound metals the most strongly, lowered blood pressure acutely in hypertensive but not in normotensive rats, especially compounds containing sulfhydryl and nitrogen ligands. Other compounds were either depressor in both types of animals or inactive. Salts of some transitional metals were active; among the pressor metals were vanadyl, manganous, nickel, and cadmium ions. Iron, cobalt, copper, zinc, and chromium ions were depressors, but only zinc had a differential action, affecting hypertensive but not normotensive levels of blood pressure.

Tipton and her colleagues while analyzing human autopsy tissues for 29 stable isotopes by emission spectrography as a guide to determining maximal permissible doses of radionuclides, found large amounts of cadmium in the American human kidney. In order to ascertain whether or not all human kidneys have such large amounts of cadmium, tissues from still-born and newborn infants, tissues from African natives relatively unexposed to modern civilization, and tissues from subjects in the Orient and Middle East exposed to differing civilizations, were collected. Some 180,000 analyses on more than 400 subjects were made.

The following results appeared: (1) infants had no detectable cadmium in their kidneys or other tissues; (2) Orientals generally had more renal cadmium than did Americans; (3) Africans generally had considerably less renal cadmium than did Americans, especially those from the Eastern Highlands; (4) levels of cadmium increased in human kidneys with age but declined in old age (fig. 1). Lead also increased with age in most tissues, later declining; chromium declined precipitously from birth to the second or third decade of life and thereafter, except in the lung, where it rose, probably from airborne chromium; tin increased in the heart with age. The essential trace metals manganese, copper, and zinc were concentrated in the infant, declined somewhat in concentration and then remained remarkably constant in tissues throughout life except for renal zinc which followed the curve of cadmium.

Basic data on the physiological roles of most of the trace elements found by Tipton and her colleagues in human tissues were lacking. The essentiality of manganese, iron, cobalt, copper, and zinc as micronutrients had been established, but the functions of such elements as titanium, vanadium, chromium, nickel, gallium, germanium, arsenic, zirconium, niobium, molybdenum, cadmium, tin, antimony, tellurium, and lead were largely unexplored. Was one or more of them essential to optimal mammalian health? Were homeostatic mechanisms operative for some or all of these elements or did one or more accumulate in human tissues with age? If a metal accumulated with age, could it influence or cause a chronic disease or a metabolic abnormality leading to a chronic disease? Could accumulation of an abnormal metal be related to the mean rise of blood pressure with age, the mean rise of circulating cholesterol with age, the increase in the incidence of diabetes mellitus with age, the increase in the severity of atherosclerosis with age, and the appearance of metaplasia?

Environmental Control of Trace Metals

To obtain basic data, an attempt was made to duplicate in small mammals for their lifetimes the experiment civilized man has inadvertently performed on himself, to observe the results in terms of chronic diseases, if any, and to analyze their tissues for metals and their accumulation with age. On a mountain top in Vermont was built an animal laboratory of wood, as metal-free as possible. Building materials were analyzed for lead and...
cadmium. Spring water was doubly deionized; air was electrostatically filtered to remove airborne contaminants from motor vehicle exhausts. Polyethylene and acrylic plastic were used throughout. Precautions to avoid metallic contamination were extensive. Rats and mice were fed, from weaning until death, a diet low in most trace metals, composed of seed rye, powdered skim milk, and corn oil; groups of 100 or more were given traces of single metals in drinking water until they died. Under these environmental conditions, two major chronic diseases, arterial hypertension and diabetes mellitus, have appeared in our laboratory.

Cadmium Hypertension in Rats

We have raised several thousand rats and mice with little or no detectable cadmium in their tissues, indicating that cadmium is probably not an essential micronutrient for these mammals. When rats were given traces of cadmium in drinking water (5 μg/ml) from the time of weaning, hypertension began to appear after about a year and increased in incidence with age. Once hypertensive, the rats remained so until death. This disorder was similar to its human counterpart, in that the incidence in females was greater than in males, the mortality among males with hypertension was greater than that among the females, both sexes had decreased

Figure 1

Mean concentrations of cadmium and zinc and the ratios of cadmium to zinc by weight, in the kidneys of 221 subjects from the United States according to age. Ranges were wide about each mean. After age 30, 18.4% of 136 persons had ratios below 0.50, whereas 22.0% of persons had ratios of 0.80 or greater and 5.9% greater than 1.0. A ratio of 0.80 or greater was usually associated with death from the consequences of hypertension. The declines in renal cadmium and the Cd:Zn ratios after age 60 are compatible with the theory that a high ratio or excess renal cadmium decreases longevity. There is no evidence that the kidneys of older persons lose cadmium; none was detected in infants. The correlation coefficient (r) of renal cadmium and zinc was 0.70 (P<0.001), and of renal cadmium with age was 0.35 (P<0.001). Reproduced by permission of the publisher of Journal of Chronic Disease.
median life spans compared to cadmium-free controls,\textsuperscript{21} of 156 and 140 days, respectively ($P < 0.005$), aortic lipids were increased, and the incidence of spontaneous aortic plaques were sizeable,\textsuperscript{24} although less than in the human disease. Hearts were enlarged, renal arteriolar sclerosis was found frequently, considerable cadmium was present in kidneys, and some of the systolic blood pressures were over 260 mm Hg.\textsuperscript{28} Incidences of hypertension in the controls and in rats given cadmium or lead were low and accompanied pyelonephritis or hydropnephrosis, which was unusual in our strain of rats. Normotensive rats given cadmium had higher levels of blood pressure than did their "cadmium-free" controls (table 1). Mice showed similar changes in mortality and life-span.\textsuperscript{20}

This study was repeated: half of 40 rats being also supplied with "hard" or calcium-containing water and the other half, with "soft" water. Eighty per cent of the animals receiving "soft" water were hypertensive by 500 days of age, whereas only 17.7\% of those receiving "hard" water exhibited the disease. Analyses of their kidneys showed that the hypertensive rats had mean cadmium-zinc ratios of 1.02 ± 0.11 and the normotensive rats had ratios of 0.35 ± 0.18 (SEM), by weight.

In a third study, nine of 22 female rats given cadmium in water from the time of weaning became hypertensive at 400 days of age, an expected number.* An attempt was made to displace the cadmium accumulated in their kidneys by zinc, using a chelating agent with 5.7 times the affinity for cadmium as for zinc, and chelated to zinc. One week after a single injection of this agent, 2-diaminocyclohexane disodium zinc tetra-acetate (di Na-Zn-CDTA), all hypertensive rats were normotensive, mean blood pressure falling from 169 ± 13.4 mm Hg to 82.8 ± 5.6 mm Hg (SEM).\textsuperscript{25} This agent was not toxic, and the rats remained normotensive and healthy for 6 weeks, despite being fed cadmium. Five months later, hypertension (B.P., 189 ± 26.2 mm Hg) had recurred in four animals, whereas the remainder were still normotensive (B.P., 75 ± 4.4 mm Hg).

A fourth study involved direct intraperitoneal injection of cadmium acetate into rats, in doses below the LD\textsubscript{50}.\textsuperscript{26} The dose exceeded the total body cadmium of rats absorbing it slowly by mouth for 3 years and resulted in a high mortality rate during the next 2 months. All of 24 survivors showed hypertension, and deaths were largely caused by internal hemorrhage. Mean blood pressures were higher than in rats with partial constriction of one renal artery. Blood pressure, measured in five rats, rose a mean value of 47 mm Hg within a half hour of the injection. When the cadmium hypertensive rats were given the zinc chelate 5 weeks later, blood pressures declined to normal levels, but more slowly than in the cases of the rats receiving cadmium by mouth.\textsuperscript{25} Analyses of their kidneys and livers showed that expected concentrations of cadmium were not found after injection of the chelate, and that the cadmium-zinc ratios were lower than in those given the cadmium alone (table 2). Smaller doses of cadmium appeared to elevate the blood

\*At 540 days of age, five additional rats had become hypertensive.

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**Table 1**

<table>
<thead>
<tr>
<th>Effect of Ingestion of Cadmium (5 µg/ml) in Drinking Water on Systemic Blood Pressure of Normotensive Rats</th>
</tr>
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<tbody>
<tr>
<td></td>
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<tr>
<td>------------------</td>
</tr>
<tr>
<td><strong>Males</strong></td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Cadmium</td>
</tr>
<tr>
<td>Control</td>
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<tr>
<td>Cadmium</td>
</tr>
<tr>
<td><strong>Females</strong></td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Cadmium</td>
</tr>
<tr>
<td>Cadmium</td>
</tr>
</tbody>
</table>

\*Differs from control group, $P < 0.005$.
†Differs from control group, $P < 0.05$.

Note: Hypertensive rats, that is, those with systolic pressures $> 142$ mm Hg, were excluded from these data. Rats were fed cadmium from the time of weaning. No controls were hypertensive.

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pressure to higher, but still “normotensive” levels (table 3).

From analyses for cadmium and zinc in the kidneys and livers of 90 hypertensive and normotensive rats, one could predict with reasonable accuracy whether or not hypertension had been present in an animal. Neither the concentration of cadmium nor that of zinc were good indices, but the renal ratios of the two metals correlated reasonably well with the level of blood pressure. When the ratio of cadmium to zinc by weight was more than 0.64, or more than 0.37 on a molar basis, the animal was sometimes hypertensive. When it was 0.80 or more (0.46 on a molar basis), the animal was always hypertensive.26 Hepatic levels and ratios were not significant in this respect. Rats fed a commercial diet which contained cadmium had a mean renal ratio of 0.52 by weight. It appeared that more than two atoms of renal cadmium to five atoms of zinc were necessary to induce hypertension.

Therefore, we have established that rats fed or given by injection small doses of cadmium become hypertensive, that removal of some of the cadmium results in a return to

<table>
<thead>
<tr>
<th>Table 2</th>
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<tbody>
<tr>
<td><strong>Mean Molar Ratios of Cadmium and Zinc in the Kidneys of Cadmium Hypertensive and Normotensive Female Rats, Treated with CDTA-Zinc</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of rats</th>
<th>Dose of Cd (mg/kg)</th>
<th>B.P.* (mm Hg)</th>
<th>Ratio Cd:Zn†</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>10</td>
<td>0</td>
<td>98 ± 4.2</td>
<td>0.30</td>
</tr>
<tr>
<td>Treated, CDTA-Zn</td>
<td>9</td>
<td>—</td>
<td>118 ± 8.5</td>
<td>0.14</td>
</tr>
<tr>
<td>Injected, Cd</td>
<td>10</td>
<td>1.5</td>
<td>140 ± 7.2</td>
<td>0.52</td>
</tr>
<tr>
<td>Treated, CDTA-Zn</td>
<td>10</td>
<td>1.5</td>
<td>96 ± 7.4</td>
<td>0.27</td>
</tr>
<tr>
<td>Controls, “cadmium free”</td>
<td>10</td>
<td>0</td>
<td>84 ± 5.7</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Injected, Cd</td>
<td>9</td>
<td>0</td>
<td>156 ± 8.6</td>
<td>0.44</td>
</tr>
<tr>
<td>Treated, CDTA-Zn</td>
<td>5</td>
<td>2.0</td>
<td>107 ± 6.1</td>
<td>0.29</td>
</tr>
<tr>
<td>Injected, Cd</td>
<td>2</td>
<td>3.0</td>
<td>166 ± 14.2</td>
<td>0.55</td>
</tr>
<tr>
<td>Treated, CDTA-Zn</td>
<td>4</td>
<td>3.0</td>
<td>87 ± 8.8</td>
<td>0.24</td>
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</tbody>
</table>

*Data computed from reference 25.
†Coefficient of correlation (r) of mean systolic blood pressure and renal ratio of cadmium to zinc, 0.78, P < 0.01.

<table>
<thead>
<tr>
<th>Table 3</th>
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<tr>
<td><strong>Effect of Injection of Cadmium on Systolic Blood Pressure of Female Rats</strong></td>
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<table>
<thead>
<tr>
<th>No. of rats</th>
<th>B.P. (mm Hg)</th>
<th>% Elevated†</th>
<th>Remarks</th>
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</thead>
<tbody>
<tr>
<td>Experiment 1</td>
<td>Controls</td>
<td>8</td>
<td>79 ± 3.4</td>
</tr>
<tr>
<td>Controls</td>
<td>12</td>
<td>84 ± 5.7</td>
<td>0</td>
</tr>
<tr>
<td>Cadmium, 2 mg/kg</td>
<td>29</td>
<td>124 ± 7.4§</td>
<td>31</td>
</tr>
<tr>
<td>Cadmium, 3 mg/kg</td>
<td>16</td>
<td>204 ± 12.4§§</td>
<td>100</td>
</tr>
<tr>
<td>Experiment 2</td>
<td>Controls</td>
<td>20</td>
<td>87 ± 4.5</td>
</tr>
<tr>
<td>Cadmium, 1 mg/kg</td>
<td>10</td>
<td>117 ± 6.5§</td>
<td>20</td>
</tr>
<tr>
<td>Cadmium, 2 mg/kg</td>
<td>9</td>
<td>156 ± 8.6§§</td>
<td>78</td>
</tr>
</tbody>
</table>

*Rats were anesthetized (Pentobarbital sodium) and warmed. Blood pressure measured by sensitive microphone on tail 1 to 3 weeks after injection of cadmium acetate. Data from reference 26.
†Elevated > 3 standard deviations above control.
§Differs from control value, P < 0.005.
§§Differs from level after 1 injection, P < 0.001.
normotension, and that a high ratio of renal cadmium to zinc is usually associated with hypertension.

Perry and Yunice have recently shown that cadmium is an intense vasoconstrictor agent when injected intra-arterially into rats in doses of 10 to 40 µg/100 g body weight, whereas larger doses (80 to 320 µg/100 g) were depressor. Pařízek has produced toxaemia of pregnancy in rats by injecting cadmium in doses similar to ours. Under many conditions, cadmium acts as an antimalbolite for zinc. Cook and Lee have demonstrated that cadmium ion inhibits the activity of angiotensinase found in blood.

Among the 400 human subjects analyzed by Tipton and associates were 34 who had hypertensive deaths, mainly from cerebral hemorrhage. When the data on their kidneys were subjected to statistical analysis, a high cadmium level or a high ratio of cadmium to zinc appeared in most of them, comparable to the values in hypertensive rats given cadmium. Subjects dying of a variety of other conditions, including accidents, had lower renal ratios of cadmium to zinc. Of subjects dying of malignant hypertension with renal failure, five of seven had low values of both cadmium and zinc, presumably due to loss of renal tissue. Several years prior to this study Perry and I found that the urine of hypertensive patients contained some 40 times as much cadmium as did urine of normotensive subjects. Cadmium levels in human blood follow a two-population curve. However, most human beings absorbing large quantities of cadmium from industrial dusts into lungs do not exhibit excessive incidences of hypertension (personal communication from M. Piscator) probably because the dose response curve is parabolic, that is, a small amount has one effect, whereas more has the opposite effect, a phenomenon common to all the trace metals studied.

As these data fulfill Koch's postulates modified for a chronic disease, it appears that cadmium may be the unknown factor responsible for cases of hypertension in the human which are not dependent upon hypersecretion of the adrenal cortex or medulla, partial obstruction of renal or carotid arteries, organic renal disease, or other obvious conditions with which elevated blood pressure is associated; in other words, so-called "essential hypertension." It is also possible that renal cadmium may raise normal blood pressure levels, as it does in rats.

Sources of Environmental Cadmium

Cadmium is present in varying quantities in foods, water, beverages, and air. Most of it occurs as a contaminant; man is the only mammal known accumulating cadmium in the kidneys to this extent, and uncivilized man accumulates little (the domestic horse may be an exception). Cadmium occurs in commercial zinc and alloyed copper.

The daily intake of man has been measured at 200 to 400 µg cadmium per day, with wide variations depending upon types of foods and waters. Tea and coffee contain 10 to 50 µg per liter. The use of phosphate fertilizers which contain 5 to 10 parts per million (ppm) of cadmium has induced some growing vegetables and grains to take up cadmium from soil. Most oysters are excellent sources, as are other mollusks and crustaceans; oysters may concentrate the metal 10,000 to 100,000 times from sea water. Soft lake water in our area accumulated cadmium from mains and copper or galvanized pipes to the extent that

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*Median molar ratios of cadmium to zinc in the kidneys of 187 American and 119 foreign subjects, according to major cause of death were: hypertension, U. S. 0.45, foreign, 0.58; accidents, U. S. 0.36, foreign, 0.38; arteriosclerotic heart disease, U. S. 0.36, foreign, 0.28; miscellaneous, U. S. 0.32, foreign, 0.32; malignant disease, foreign, 0.29; chronic infections, foreign, 0.28. The differences between hypertensive and other values were significant (P < 0.01 to < 0.005).

†Cadmium may be the unknown factor that converts a temporary vasoconstrictive reaction to stress into a permanent one. Partial constriction of a renal artery and organic renal diseases may also act in this way.
half of the tap waters we have analyzed exceeded the allowable Public Health Service standards of 10 ppb. Water, however, contributes but 5 to 10% of the total intake and that only after standing in pipes.

The practice of refining wheat and polishing rice may alter the relative amounts of cadmium and zinc contained in the finished grain (table 4). Cadmium is distributed throughout the endosperm and germ; zinc is concentrated in the germ and bran. Refined white flour contained only 28% of the zinc in the whole grain, all of it bound to gluten, but cadmium was not removed by refining. In rice, cadmium was found firmly bound to glutelin, and the concentration in ash rose sharply with polishing.

Refined wheat flour has a ratio of cadmium to zinc of 1:17 to 1:23, compared to 1:120 in whole wheat. Persons from areas of the world where the major source of calories comes from refined grains are apt to show high levels of renal cadmium.

The urinary output of cadmium approximates 30 to 40 μg per day or about 10% of the intake. About 3 μg per day is retained in the body, of which 1 μg daily is bound to the kidney, making up 10 mg at 30 years of age. The relative absorption of ionic cadmium in water as compared to cadmium bound to glutenin in grains, bound to protein in seafood, or contained in other foods is unknown.

There is good correlation with deaths from hypertensive heart disease and the softness of municipal water supplies in this country, hard water areas having considerably lower rates. Death rates are also higher in states having a seacoast than in states without; proximity to the sea generally produces more rainfall and allows the municipal use of surface water, which is characteristically soft. A good correlation has been found by Carroll with cardiovascular death rates and with the amount of cadmium in the air as an industrial pollutant. Although air can be calculated to be a relatively small source, it probably contributes to cadmium in rainwater. The cadmium in tap water coming from pipes, according to our analyses, provides an additional source.

**Diabetes Mellitus from Chromium Deficiency**

Partial dietary deficiency of chromium in rats has resulted in a moderate diabetic state characterized by elevated fasting serum glucose levels and glycosuria. Schwarz and Mertz, and Mertz and associates have shown that the low tolerance to glucose of rats on certain diets was the result of partial chromium deficiency, a defect restored by traces of trivalent chromium. With the environmental exclusion of chromium in our rat laboratory, a more severe deficiency was produced, resulting in retarded growth and diabetes mellitus. That was rapidly relieved by traces (1 to 2 μg/ml) of chromium (III) acetate in drinking water. Furthermore, by taking advantage of the demands of the rat fetus for chromium (pregnancy depleting the mother), we have raised five generations of rats which showed increasing incidence of diabetes. This strain would be considered to have an hereditary disorder were it not known to be dietary and reversed by chromium (III).

**Possible Relation of Chromium Deficiency to Atherosclerosis**

Chromium deficient rats showed at death a fairly high percentage of plaques in their aortas, especially when old. Rats given chromium for their lifetimes demonstrated three interesting findings: a significant prolongation

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Table 4

<table>
<thead>
<tr>
<th>Grades</th>
<th>Zinc (μg/g Dry Weight)</th>
<th>Cadmium</th>
<th>Chromium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheat</td>
<td>31.5</td>
<td>0.26</td>
<td>0.97</td>
</tr>
<tr>
<td>Patent flour, 61%</td>
<td>8.9</td>
<td>0.38</td>
<td>0.58</td>
</tr>
<tr>
<td>First clear flour, 11%</td>
<td>15.9</td>
<td>0.26</td>
<td>0.92</td>
</tr>
<tr>
<td>Low grade flour, 2.5%†</td>
<td>33.6</td>
<td>0.26</td>
<td>0.53</td>
</tr>
<tr>
<td>Red Dog†</td>
<td>3.6</td>
<td>0.38</td>
<td>0.99</td>
</tr>
<tr>
<td>Shorts†</td>
<td>106.0</td>
<td>0.92</td>
<td>1.20</td>
</tr>
<tr>
<td>Bran, 15%†</td>
<td>100.2</td>
<td>0.88</td>
<td>1.24</td>
</tr>
<tr>
<td>Germ</td>
<td>133.4</td>
<td>1.11</td>
<td>1.36</td>
</tr>
</tbody>
</table>

*Data from reference 17.
†Used as feed for animals.
of life span, as did mice (one rat lived 4 years), almost complete absence of spontaneous aortic plaques, and abolition of the usual rise of serum cholesterol levels with age.24 These observations are being continued with a second series of rats, but to obtain the answer requires 4 years. Chromium is an essential micronutrient for rats and mice, both for optimal growth19 and for longevity.21

Chromium Deficiency in Man

The possible influence of chromium deficiency in abnormal lipid metabolism and atherosclerosis in man is less evident than that of cadmium and hypertension, but there are a number of indirect observations which should stimulate study.

1. Tissue levels of chromium in Americans, high at birth, declined precipitously with age, and a sizeable number were deficient13 (figs. 2 and 3). Pulmonary chromium, however, rose with age, probably from airborne metal, and this rise was not reflected in increased deposits in other tissues.13 These low tissue levels of chromium were not duplicated in other mammals nor in subjects from the Orient, Africa, and the Middle East, who had 2.5 to 8 times as much in aorta, 3 to 13 times as much in brain, 2.5 to 4 times as much in heart, 2.5 to 7 times as much in kidney, twice as much in liver, 2 to 4 times as much in pancreas, 3 to 6 times as much in spleen, and 2.5 to 5 times as much in testes as did Americans.9 Furthermore, only 15 of 949 foreign tissues were devoid of chromium (1.57%), whereas 181 of 1,029 of the same tissues of Americans had no detectable chromium (17.6%, P < 0.0005). In kidney, liver, spleen, and brain 23.3% of American samples lacked chromium (<0.001 μg/g, wet weight), compared with 1.6% of foreigners (P < 0.0001). Therefore, adult Americans, according to 200 or more subjects from 10 cities, are low in tissue chromium compared to a similar number of human beings from other areas of the world.

2. There is some evidence that excessive ingestion of sugar may alter the lipids in human serum in a manner considered to predispose to atherosclerosis.47,48 There is likewise indirect evidence that excessive ingestion of sugar may influence the development of maturity-onset diabetes mellitus.49 The predisposition of atherosclerotic complications to develop in diabetic subjects has been known for 50 years. Many patients suffering from atherosclerotic disorders or elevated serum triglycerides have low tolerance to glucose meals.47,50 Some 87% of older persons examined have exhibited abnormal glucose tolerance.51,52 Consumption of sugar in the United States has been calculated at 50 kg/person/year.49

3. Evidence is accumulating that some older diabetic subjects respond to small doses of chromium (III) chloride by an amelioration of the diabetic state. Although to date only small series of patients have been treated, improvement has been noted in 40% of patients in Syracuse,52 67% of patients in Washington,53 33% of patients in Brattleboro, Vermont, and no patients in Hanover, New Hampshire (in a short-term study). Difficulties with dose, absorption, and form of salt or complex are apparent and require further study. Oral chromic chloride is poorly absorbed.54

4. Chromium may act on lipid metabolism.55 In aged persons, oral chromic acetate was relatively ineffective in altering serum cholesterol levels, only 9% reduction being observed.56 The oxidation of C14-palmitate by aortas of chromium-deficient rats, however, was stimulated.57 If this work is confirmed, it should have wide implications. The aortas of male foreign subjects contained in ash 5.5 to 15 ppm chromium and of American subjects, 1.9 ppm, 13% of whom were devoid of chromium (fig. 2). Atherosclerosis is believed to be less severe in areas where tissue chromium was high.9

Sources and Possible Losses of Chromium

There is adequate chromium in soil, although little is available to plants,13 from which come our essential mineral micronutrients. Chromium (III) in solution has the capacity to "olate," that is, to form long
chains with water molecules. In an alkaline medium, and when heated to 120 °C, olation is enhanced. It is possible that chromium in foods becomes unavailable when superheated. Although less chromium was found in refined flour than in wheat (table 4), the decrement was not large enough to account for dietary deficiencies.

An explanation for the depletion of bodily chromium in Americans may lie in the experiments of Glinsmann and associates, who demonstrated that circulating chromium rises after a glucose load by a factor of 2 to 3 in normal but not in diabetic subjects. We have found increases in urinary chromium after oral glucose loads up to 400 μg/L, the normal

<table>
<thead>
<tr>
<th>Age in Years</th>
<th>Liver ppm</th>
<th>Aorta ppm</th>
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</thead>
<tbody>
<tr>
<td>0-10</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>10-20</td>
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<tr>
<td>70-80</td>
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**Figure 2**

Mean concentrations of chromium, a trace metal essential for normal glucose metabolism, in 186 livers and 103 aortas of American subjects according to age, when present in tissues. Mean values of all adults were 0.7 and 2.0 ppm, respectively. The numbers in parentheses indicate the percentage of samples in each age group in which chromium was not detected (<0.1 μg/g ash) and not included in the mean values. Note the maintenance of hepatic birth levels up to 10 years of age and the rapid decline thereafter. Tissues of foreigners had significantly higher levels. Livers of 45 African adults had 1.3 ppm (two were deficient); of 33 Near Eastern adults, 2.4 ppm (P<0.001); of 67 Far Eastern adults, 4.6 ppm (P<0.001); of nine Swiss adults, 5.8 ppm (P<0.001) (one from Near East was deficient). Aortic concentrations were as follows: 15 Africans, 6.6 ppm (none deficient); 15 Near Eastern subjects, 11 ppm (P<0.001) (two deficient); 65 Orientals, 15 ppm (P<0.001) (two deficient); five Swiss, 8.8 ppm (P<0.001) (none deficient). It is apparent not only that a large percentage of these tissues from Americans were deficient in chromium, but that tissues from foreigners contained more than did those from Americans. (American data from Tipton and Cook; foreign data from Tipton and associates.)
amount being 4 μg/L. Hopkins has shown in the rat that the kidney clears 30% of injected $^{51}$Cr (III) in 2 hours. As the American adult contains an estimated 5 mg of chromium in his body, depletion of body stores could theoretically result from repeated insults with glucose or refined sugars having little or no chromium. Analysis of raw sugars showed appreciable amounts of chromium, whereas refined sugar had little (table 5). Most fats were good sources.

We have measured and calculated that about 200 μg of chromium/day are contained in a normal adult diet, or about 3 μg/kg of body weight. Rats and mice became deficient of 10 μg/kg of body weight/day.

![Figure 3](http://circ.ahajournals.org/)

**Figure 3**

Mean concentrations of chromium, when present, in 135 spleens and 176 kidneys of American subjects according to age. Mean values of all adults were 0.5 and 1.0 ppm, respectively. Note the maintenance of the renal birth level up to age 10 years and the sharp decline thereafter. The numbers in parentheses indicate the percentage of samples in each age group deficient (<0.1 μg/g ash) in chromium and not included in the mean values. Adult foreign concentrations were significantly higher as follows: Spleen, 40 Africans, 2.2 ppm; 34 Near Eastern subjects, 5.5 ppm (P<0.001); 62 Orientals, 3.1 ppm (P<0.001); eight Swiss, 4.5 ppm (P<0.001) (two Orientals deficient). Kidney, 48 Africans, 3.3 ppm; 31 Near Eastern subjects, 13 ppm (P<0.001); 66 Orientals, 24 ppm (P<0.001); nine Swiss, 17 ppm (P<0.001) (none deficient). In the tissues of a large percentage of American subjects, chromium deficiency existed and most foreigners had larger amounts. (American data from Tipton and Cook; foreign data from Tipton and associates.)
Possible Influence of Drinking Water on Death Rates from Atherosclerosis

The correlation of death rates from hypertensive and atherosclerotic heart disease with some factor associated with the degree of softness of municipal water supplies in the United States, using 1949-51 rates and water analyses, was confirmed for 1960 rates and waters, and in the interval, was demonstrated in Great Britain and Sweden. A similar correlation of death rates from cerebral hemorrhage and acidity of river water has been found in Japan. Correlations of the type of water with rates from vascular lesions of the central nervous system, however, were poor. In reviewing the data, we have come to the conclusion, tentatively, that deaths from cerebral thrombosis, and perhaps other peripheral atherosclerotic complications, are not associated with the type of potable water. Furthermore, no significant correlations were found with cardiovascular death rates and chromium in municipal water, nor with chromium in water and deaths from diabetes mellitus. The most significant associations were between the two types of heart disease and the degree of softness of water, which may reflect the uptake of cadmium from pipes. Atherosclerotic heart disease often has a hypertensive component, which may explain this association.

Conclusions

Trace elements are important catalysts for many biological processes, most of them still unknown. They all come from soil or sea. Implications for microbiology, nutrition, pharmacology, biochemistry, and even molecular biology are becoming apparent.

Man's use of metals has exposed him to a number of extraneous elements by introducing them into food, water, and air, and to which he and other mammals have little or no ability to adapt. Chronic diseases may result from these lifetime exposures, diseases which are not prevalent in more primitive societies. They may arise especially from those abnormal elements which accumulate with age from excessive exposures, or from those essential elements which decline because of conditioned dietary deficiencies.

One common form of hypertension is probably an example of accumulation of cadmium in the kidney; deficiency of chromium may influence glucose and lipid metabolism and affect atherosclerosis. These observations do not exclude the involvement of other elements in both diseases.

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CADMIUM AND CHROMIUM

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