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Cadmium Effects in Rats on Tissue Iron, Selenium, and Blood Pressure; Blood and Hair Cadmium in Some Oregon Residents

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Exposure of rats to cadmium causes a marked depletion of iron in liver and kidney. Selenium neither counteracts or intensifies the influence of cadmium on tissue iron levels. Selenium injections protect against cadmium-induced testicular damage but cause this element to accumulate in the testes at higher concentration than in animals exposed to cadmium without selenium. Selenium injection diverts the binding of cadmium from low molecular weight proteins to high molecular weight ones. Dosing rats with selenium and cadmium or inclusion of Se or Cd in the diet did not result in altered cadmium binding in tissues, raising some questions concerning the environmental significance of these injection experiments. Addition of selenium to a diet containing cadmium decreased the accumulation of cadmium in liver and kidney, but increased its deposition in testes. The metabolism of cadmium bound to metallothionein was markedly different as compared to the inorganic salt of this element. Dietary ascorbate, but not citrate or cysteine, decreased the deposition of cadmium in rat tissues. In some low-level exposure experiments with cadmium (1 to 1000 ppb), no differences were found in the percentage of dose absorbed or rate of cadmium accumulation when provided in food versus water. Female rats tended to absorb more cadmium than males. The binding of cadmium to cytosolic proteins was found to be different between rats fed low levels of cadmium (up to 1 ppm) as compared to those fed high levels of this element (100 ppm). Cadmium was not found to contribute to hypertension in rats, and a summary of results by various investigators is presented.

Blood and hair cadmium levels in Oregon residents were found to be highest in employees of a mine, and hair cadmium was found to be respectively higher in smokers than nonsmokers and in metal workers than office workers. No relationships were observed in humans between blood or hair cadmium levels and blood pressure.

Cadmium is an industrial product or by-product which is of environmental concern. It is used in many industrial processes, such as a constituent of easily fusible alloys, soft solder, electroplating, deoxidizer in nickel plating, engraving processes, electrodes for vapor lamps, photoelectric cells, and nickel-cadmium storage batteries (*1*, *2*). Therefore, there can be many industrial hazards due to this element. Concentration of cadmium has been reported to be higher in air of industrial cities (*3*), thus providing a possible environmental hazard. Cadmium poisoning has been reported from foods which had been kept or prepared in cadmium-plated containers and has occasionally be found in drinking water in unacceptable levels. Cadmium, in contrast to many other elements, accumulates with age in tissues (*3*). Very little renal cadmium is present at birth, but relatively large amounts of this element are present in kidneys of adults (*4*), the concentration in newborn being less than 1% of adults. Thus, this pattern is suggestive of environmental exposure.

In our studies, we have investigated the influence of cadmium on iron and selenium metabolism. Since cadmium has been reported to contribute to hypertension (*5*, *6*), the influence of this element on blood pressures was investigated in rats. A survey was made on the blood and hair cadmium levels in Oregon residents living in different parts of the state

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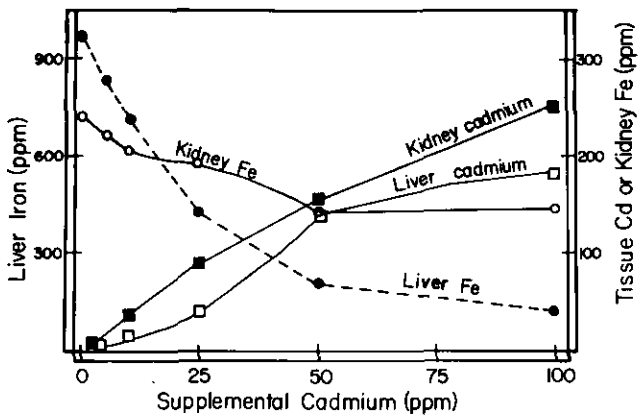

FIGURE 1. Effect of dietary cadmium on iron levels in liver and kidney of rats. Weanling rats (3 male and 3 females/diet) were fed a basal casein diet (*11*) or this diet plus 2.5, 5, 10, 25, 50, and 100 ppm cadmium for 12 weeks.

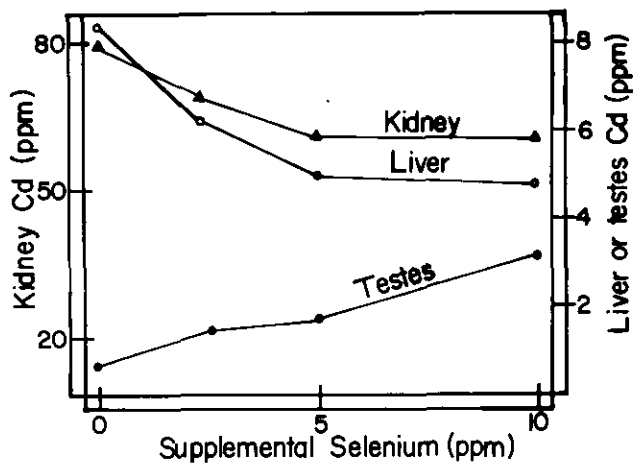

FIGURE 2. Effect of dietary selenium on cadmium levels in liver, kidneys, and testes. Weanling male rats were fed ground Purina Rat Chow containing 100 ppm cadmium or this diet plus either 2.5, 5.0, or 10 ppm selenium for 8 weeks.

and of people involved in various occupations. Correlations between blood or hair cadmium levels and hypertension were determined.

As shown in Figure 1, cadmium markedly depressed the iron concentrations in liver and kidney of rats. A linear decrease occurred up to 50 ppm after which a plateau was reached. This depression of tissue iron by cadmium is in agreement with other work (*7–10*). Cadmium has been shown to involve the loss of iron mainly from ferritin (*8*), which is consistent with work from my laboratory showing cadmium to depress iron levels more in the soluble fraction than other cellular fractions (*11*).

Selenium will protect against cadmium-induced testicular damage as discussed by Diplock (*12*). Therefore, it was of interest to determine the influence of selenium on cadmium metabolism. As indicated in Figure 2, selenium decreased the accumulation of cadmium in liver and kidney, but caused an accumulation of this element in the testes. A proportional increase of cadmium in the testes occurred with each increase of dietary selenium, whereas the depression of cadmium in liver and kidney by selenium reached a plateau at 5 ppm.

The results shown in Figure 3 indicate that selenium does not counteract or worsen the effect of cadmium in depressing tissue iron levels. Thus, the beneficial effects of selenium against cadmium is by other means.

Selenium was shown to divert the binding of cadmium in testes cytosols, and this was suggested as a possible way this element counteracted the damaging effects of cadmium (*13*). We extended these studies to determine whether injected selenium would divert the binding of injected cadmium in other tissues. In addition to the testes, selenium was found to also divert the binding of cadmium in kidney and plasma, but not very much in the liver (*14*). Thus, the interaction of selenium and cadmium is tissue-dependent. An example of the influence of selenium on cadmium binding in the kidney cytosols is shown in Figure 4.

In the reverse situation, cadmium was not found to have any influence on either the activity of the

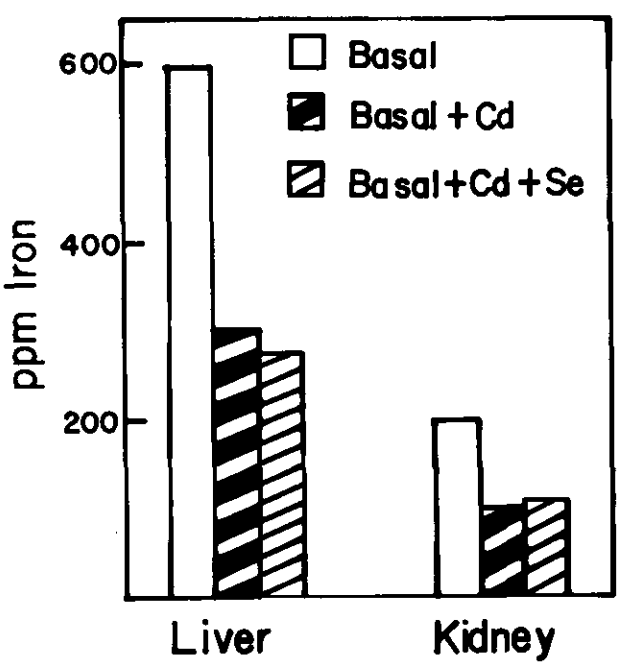

FIGURE 3. Effect of dietary selenium and cadmium on liver and kidney iron content. These are the same rats described in Figure 2. The data are shown for rats fed 5 ppm selenium in the diet, but other levels of selenium gave similar responses.

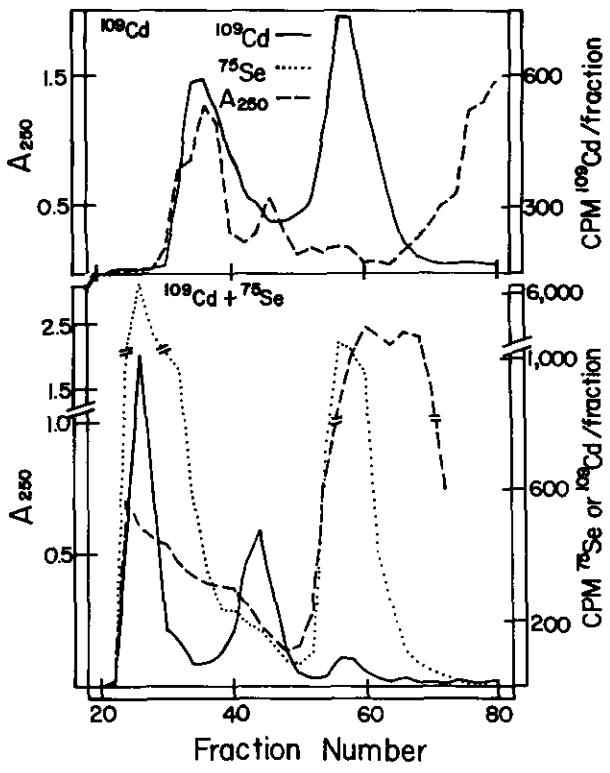

FIGURE 4. Influence of selenium pretreatment on cadmium binding to proteins in kidney cytosol. Male rats (200 g) which had been fed Purina Chow were injected intraperitoneally with 50 μCiCd^{109} plus 2 mg cadmium per kg body weight as the chloride (upper graph) or with this plus 50 μCi ^{75}Se and 1.42 mg selenium as sodium selenite/kg body weight at another site (lower graph). The rats were killed 2 hr after injection, and the kidneys homogenized (1 g/2 ml) in 0.05*M* Tris, pH 8.4. The cellular components were centrifuged out by differential centrifugation and the cytosol eluted through G-75 Sephadex columns (2 × 90 cm) at a flow rate of 24 ml/hr with 0.05*M* Tris, pH 8.4. About 4 ml was collected per fraction.

selenoenzyme, glutathione peroxidase, or on the tissue selenium content (*15*). However, cadmium has been shown to alter selenium metabolism (*12*).

The environmental significance of these injection experiments, however, is questionable, since either oral dosing of selenium and cadmium or inclusion in the diet do not cause a diversion of cadmium binding in tissues (*15*). Since animals (and man) are exposed to heavy metals in the environment either through the oral or pulmonary route, selenium must counteract metals such as environmental cadmium by other mechanisms besides diverting their binding in tissue proteins. It should be emphasized that cadmium-induced testicular damage is brought about when this element is injected and not when it is given orally. Thus, the protection by selenium of testicular damage due to injected cadmium could be by diverting its binding in this tissue. This accumulation of cadmium in testes as the result of selenium may also suggest that tissue cadmium concentrations alone cannot be used to assess possible toxicity under all circumstances.

Metallothionein (MT) is a protein which binds cadmium (*16, 17*). Since the binding of metals by MT has been advocated to be the way it counteracts heavy metal toxicity, an experiment was conducted to determine if thionein, the metal free MT, would prevent the testicular damage due to cadmium. Thionein (25 mg/kg) was injected intraperitoneally into rats (200 g) 15 min before ^{109}Cd (500 μCi/kg) and cold cadmium (0.01 mmole/kg) injections. Two days afterwards the rats were killed and the testes examined for swelling and hemorrhages. However, thionein was not found to protect the testes against cadmium damage, but caused an unusual distribution of cadmium among the tissues. This prompted a study on the metabolism of cadmium bound to MT. Interestingly, about 60% of the dose of cadmium with MT was deposited in the kidneys (Table 1). Thus, even though MT was purified from the liver, the cadmium was deposited predominantly in the kidneys. In contrast, the liver contained most of the cadmium when a cadmium salt was injected. The other tissues (blood, heart, spleen, and testes) of the cadmium chloride injected rats also contained more cadmium than the MT-injected rats. The greater urinary content of cadmium in the MT-injected rats is probably due to this greater deposition in the kidneys. This indicates that the "form" of cadmium has a pronounced effect upon its metabolism. Simi-

Table 1. Comparative metabolism of cadmium chloride or cadmium bound to thionein.[a]

	Distribution of dose, %[b]		
Tissue	$^{109}CdCl_2$	^{109}Cd MTP_I	^{109}Cd MTP_{II}
Blood	0.20 ± 0.27	0.016 ± 0.004	0.004 ± 0.003
Heart	0.11 ± 0.11	0.013 ± 0.003	0.011 ± 0.001
Kidneys	1.68 ± 0.52	60.4 ± 1.51	63.5 ± 2.25
Spleen	1.75 ± 1.1	0.028 ± 0.006	0.037 ± 0.004
Testes	0.77 ± 0.48	0.064 ± 0.014	0.073 ± 0.004
Liver	32.45 ± 16.7	3.58 ± 1.28	2.51 ± 0.15
Urine	0.03 ± 0.02[c]	9.89 ± 1.50[c]	14.0 ± 1.94[c]
Feces	—	0.162 ± 0.033[d]	0.186 ± 0.034[d]

[a] All rats were killed 24 hr after injection. Cadmium-thionein (1 mg) was injected intraperitoneally in rats (200 g). The same amount of cadmium chloride was used to equal the amount of cadmium in the MT preparations. The cadmium thionein was purified from livers of rats which had been fed 100 ppm cadmium in the diet for 4 weeks and injected with 500 μCi ^{109}Cd/kg body weight 24 hr before they were killed. The cadmium-thionein species (MTP_I and MTP_{II}) were purified by gel filtration (G-75 Sephadex), ion exchange resin (DEAE cellulose) and hydroxylapatite chromatography.

[b] Percent of dose (means of four rats ± standard errors).

[c] Percent of dose in 24 hr urine.

[d] Percent of dose/g feces.

Table 2. Effect of dietary ascorbate, citrate, and cysteine on tissue cadmium and iron levels in rats fed diets containing cadmium.[a]

Diet	Testis[b]		Liver[b]		Kidney[b]	
	Cd, ppm	Fe, ppm	Cd, ppm	Fe, ppm	Cd, ppm	Fe, ppm
Cadmium	3.2 ± 0.4[c]	75.3 ± 10.8	8.0 ± 1.4	194.3 ± 48.9[d]	90.7 ± 22.0	20.1 ± 7.0[d]
Cadmium + ascorbate	2.1 ± 0.3[d]	100.6 ± 15.1	5.1 ± 1.4[d]	263.8 ± 59.5[d]	73.1 ± 10.9[d]	37.3 ± 5.7[c]
Cadmium + citrate	3.1 ± 0.8[c]	72.4 ± 19.1[d]	14.7 ± 6.3[c]	182.5 ± 48.1[d]	109.8 ± 22.2[c]	23.7 ± 4.8[d]
Cadmium + cysteine	3.1 ± 0.8[c]	110.2 ± 12.6	9.0 ± 3.6	273.9 ± 100.3[c]	92.6 ± 25.1	36.5 ± 9.5[c]
Cadmium + ascorbate + citrate	2.1 ± 0.2[d]	97.1 ± 8.4	5.7 ± 1.9[d]	233.8 ± 90.3	84.9 ± 7.0	31.8 ± 9.9
Cadmium + citrate + cysteine	3.6 ± 0.6[c]	117.2 ± 37.2	9.5 ± 4.3	316.1 ± 137.4[c]	101.8 ± 30.0	34.0 ± 8.6
Cadmium + ascorbate + cysteine	3.2 ± 1.8[c]	163.5 ± 94.7[c]	5.5 ± 1.7[d]	366.3 ± 126.9[c]	84.2 ± 8.9	42.8 ± 14.9[c]
Cadmium + ascorbate + citrate + cysteine	2.1 ± 0.3[d]	108.4 ± 20.9	4.7 ± 1.8[d]	282.6 ± 45.4	74.8 ± 14.9[d]	32.7 ± 9.1
Basal (no additional Cd)	0.6 ± 0.2	141.4 ± 10.8	0.2 ± 0.01	348.2 ± 45.5	0.3 ± 0.01	51.5 ± 10.4

[a] Weanling male rats (6/diet) were fed ground Purina rat chow containing 100 ppm cadmium or this diet plus either single additions or various combinations of 1% ascorbate, citrate, or cysteine. The rats were fed these diets for 8 weeks.
[b] Mean of six determinations ± standard deviation.
[c, d] Values within a column are significantly different.

lar patterns have been obtained by other workers on the metabolism of MT (*18*). However, additional work needs to be done on the metabolic fate of the protein moiety.

A few years ago a commercial product containing cysteine and citrate was marketed and claimed to decrease the absorption of heavy metals. Ascorbate has been shown to decrease the accumulation of cadmium in tissues and to counteract the anemia due to this element (*19*). In light of these reports and the results in Table 1, an experiment was conducted to study the influence of ascorbate, citrate, or cysteine alone or in various combinations on cadmium accumulation and iron content of tissues. In all tissues, dietary ascorbate either alone or in combination with citrate resulted in a reduced accumulation of cadmium in tissues (Table 2). The addition of cysteine reduced the effectiveness of ascorbate in reducing cadmium accumulation. Ascorbate appeared to be just as effective alone as compared to its combination with citrate. In fact, citrate alone caused an accumulation of cadmium, particularly in liver and kidney. A slightly different pattern is apparent for the iron levels. The combination of ascorbate and cysteine was most effective in causing iron accumulation. Citrate had the most depressing effect on the accumulation of iron, but this was counteracted to a certain extent by ascorbate or cysteine. Thus, ascorbate alone appears to be most effective in reducing the concentration of cadmium, but this compound plus cysteine are most effective in causing an accumulation of iron.

Some low-level cadmium exposure experiments are presently in progress at Oregon State University (*20*). Rats were given 1 to 1000 ppb cadmium in water or food for 1, 2, 4, 8, or 12 weeks, and the kidney was found to accumulate the highest concentration of this element. However, the liver because of its size contained from 35% to 55% of the total body burden, while the kidney accounted for 35 to 45% of this burden. No significant difference was found in the percentage of dose absorbed or rate of cadmium accumulation when the same concentration of cadmium was provided in food versus the water. Female rats tended to accumulate cadmium at a faster rate and absorb a larger percentage of the ingested dose than did male rats. Differences in binding of cadmium to the tissue cytosolic proteins were found between tissues from rats fed diets with low levels of cadmium (1 to 1000 ppb) as compared to those from rats fed a high level of cadmium (100 ppm). The results are consistent with the work of another group (*21*). This indicates that low levels of cadmium should be used in order to simulate the physiological effects of environmental levels of this element.

Since cadmium has been implicated in hypertension (*5, 6*), we conducted experiments to investigate this relationship. However, we found no significant effects of cadmium on blood pressure when rats were given cadmium in the water for 88 weeks (Fig. 5). There was an insignificant increase of about 5 mm Hg in the cadmium-fed rats between 22 and 44 weeks of age. Neither did the addition of cadmium to water for genetically hypertensive rats have any significant effect on their blood pressures (Fig. 5, insert). These results are consistent with a number of other results (*2, 23–27*), but in disagreement with two research groups (*5, 6, 22*).

The results of various investigators on the influence of cadmium on blood pressures in rats are summarized in Table 3. It is evident that the dis-

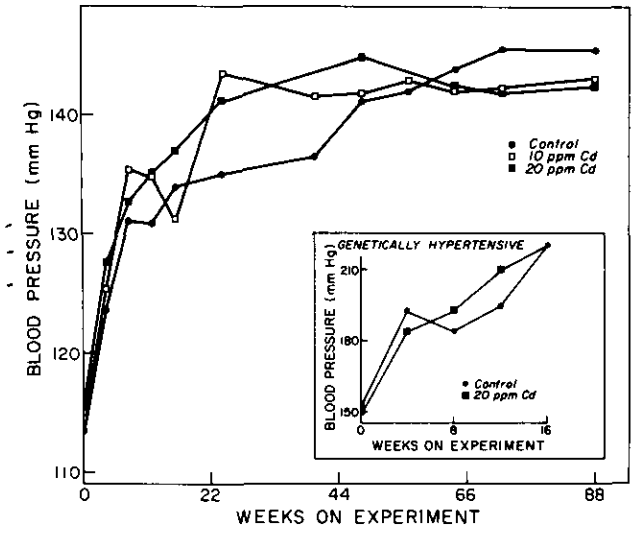

FIGURE 5. Influence of cadmium in the drinking water on the blood pressure of rats. Insert shows the influence of cadmium in the water on the blood pressure of a genetically hypertensive strain of rats. Data from Whanger (*10*).

agreement is not due to the strain of rats, the method of cadmium administration, or the doses of cadmium used. Since the two groups of investigators reporting hypertension due to cadmium used a rye flour-based diet, whereas those researchers who found negative responses used other kinds of diets this may be a contributing factor. Among the dietary factors which may contribute to this disagreement could be the levels of sodium, calcium, zinc, copper, or selenium. Thus, if cadmium contributes to hypertension, it must cause this disorder under a very limited set of conditions, which raises serious questions concerning its relationship to hypertension in the general environment.

In order to obtain some information on relationship of blood and hair cadmium levels and hypertension in people, a survey study was conducted with some Oregon residents. At the time of drawing blood, the name, age, occupation, smoking habits, water source, years at location, and blood pressure were obtained from each donor. The cadmium levels in blood and hair were highest in people living in the town of Riddle, Oregon (Table 4). Employees of the local nickel mines had significantly higher blood levels than the resident of this town or people living in other locations of the state. Cadmium is a contaminant of the nickel ore and this is probably the source of the element for these employees. No relationship between blood cadmium levels and blood pressure was found either in the employees of this mine or in residents of the various cities of Oregon. Cadmium analyses on blood from hypertensive and normotensive patients of the Veteran's Administration Hospital in Portland, Oregon, revealed no differences between these patients (Table 4). The higher blood cadmium in these patients is probably due to their age, since this element is known to accumulate in tissues of people as they grow older (*3*). Thus, blood cadmium levels were not related to hypertension, and neither were the cadmium levels of these patients correlated to renin or aldosterone levels. These data are in agreement with those of Beevers et al. (*28*), who found no difference in blood cadmium levels between normotensive and hypertensive patients of similar ages.

Schroeder (*29*) reported cadmium content to be significantly higher in kidneys, and Glauser et al.

Table 3. Summary of effects of cadmium on hypertension in rats.

Cd administered, ppm	Strain	Time, days	Diet	Hyper-tension	Investigators
0.1-10.0	Long-Evans	182-365	Rye flour based	Yes	Perry and Erlanger (*6*)
5.0	Long-Evans	180-240	Rye flour based	Yes	Schroeder et al. (*5, 22*)
5.0	Wistar	480	Commercial	No	Lener and Musil (*23*)
5.0	Long-Evans	320	Egg white based	No	Doyle et al. (*25*)
5.0	Sprague-Dawley	365	Commercial	No	Friberg et al. (*2*)
1-30	Wistar	90	Commercial	No	Loeser and Lorke (*26*)
10-20	OSU Brown	660	Casein based	No	Whanger et al. (*10*)
20	Genetically hypertensive	112	Casein based	No	Whanger et al. (*10*)
Injected 2 mg/kg	Long-Evans	120	?	Yes	Schroeder et al. (*22*)
Injected, 0.2–2 mg/kg	Sprague-Dawley	78-124	Commercial	No	Porter et al. (*24*)
Oral dose, 25–150 mg/kg	Sprague-Dawley	100	Commercial	No	Katsonis and Klaassen (*27*)

Table 4. Cadmium concentrations in blood and hair of some Oregon residents.

Town	Cd concentration[a]	
	Blood, ppb	Hair, ppm
Pendleton	3.2 ± 0.5	0.73 ± 0.34[b]
Klamath Falls	5.3 ± 3.8	0.54 ± 0.32[b]
Eugene	3.8 ± 2.4	1.31 ± 0.42
Portland	6.8 ± 4.6[e]	1.48 ± 0.42[c]
Coos Bay	5.6 ± 3.0	1.21 ± 0.39[c]
Riddle	7.8 ± 5.6[d]	1.83 ± 0.42[c]

[a] Means of 8–10 samples ± standard error.
[b,c] Significantly different ($p < 0.05$).
[d] Nickel mine employees; 20.0 ± 3.1 ppb ($p < 0.05$).
[e] V. A. Hospital (Portland); blood of hypertensive, 8.9 ± 5.0; normotensive, 9.0 ± 4.0 ppb.

Table 5. Effects of occupation on hair cadmium levels in some Oregon workers.[a]

Occupation	Hair, ppm[b]
Metal workers (welders, sheet metal workers, electroplating, etc.)	1.68 ± 0.44[c]
Laborers (no metals in occupation)	1.39 ± 0.43
Office workers	0.96 ± 0.39[d]

[a] Smokers, 1.66 ± 0.45 ppm; nonsmokers, 0.90 ± 0.38 ppm ($p < 0.05$).
[b] Means ± standard error.
[c,d] Significantly different ($p < 0.05$).

(*30*) reported the cadmium levels to be higher in blood of hypertensive than normotensive humans. However, in both of these studies the hypertensive people were about 10 years older than the normotensive ones, and this difference in all probability is an age effect. This possibility is supported by the data of Morgan (*31*), who found no difference in renal cadmium content between control and hypertensive patients of similar ages.

When the blood and hair cadmium data were recalculated and comparisons made with respect to smoking habits or occupations, differences were also found. The hair cadmium content was highest in metal workers, intermediate in laborers not using metals in their occupation, and lowest in office workers (Table 5). Hair cadmium levels were found to be higher in smokers than nonsmokers, indicating this factor must be taken into consideration in studies of this type. No differences were found in blood cadmium levels either between smokers and nonsmokers or between people of the various occupations. This blood cadmium pattern of smokers and nonsmokers, however, is inconsistent with other data (*28*). These blood levels no doubt depend upon the smoking patterns of the subjects, and this may be the reason for disagreement.

In conclusion, since cadmium causes a marked depression in tissue iron levels and ascorbate decreases the accumulation of cadmium in tissues, I would like to propose that people exposed to this element should elevate their intake of iron and ascorbate. Although more data are needed, the present information would suggest beneficial effects would be obtained. The data indicate that neither citrate or cysteine improves the beneficial effect of ascorbate. Cadmium accumulates in tissues at higher concentration in animals given cadmium plus selenium than in those given just cadmium, but cadmium is less toxic in the first group. Therefore, more information is needed to distinguish between tissue cadmium which is toxic and that which is not toxic. This suggests that tissue cadmium content alone cannot be used under all circumstances to assess toxicity.

Injection experiments need to be confirmed by those in which the test agent is administered orally or by the pulmonary route. Different results have been obtained when administration of test materials is by injection compared to ingestion. Since animals are exposed in the environment by the oral or pulmonary routes, results must be obtained by these routes to simulate environmental conditions.

Another point which should be made is that more low-level long-term experiments need to be conducted. It can no longer be assumed that high exposure for a short term is similar to low exposure over a long term. The difference in binding of cadmium in tissues from animals fed 100 ppm cadmium in the diet for a short period as compared to those fed 1 ppm cadmium in the diet for several months is an example. Similar patterns have also been noted for mercury in my laboratory. Therefore, chronic exposure to chemicals at concentrations likely to be found as the result of environmental contamination is necessary to simulate the physiological effects under environmental conditions.

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