Some Effects of Oral Ingestion of Cadmium on Zinc, Copper, and Iron Metabolism

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Data are presented to show that ingestion of cadmium chloride by rats at low levels leads to alteration of zinc metabolism in the liver, even though the formation of metallothionein is not evident. A dose–response relationship between amount of cadmium ingested and degree of perturbation of zinc metabolism in liver was found. Oral cadmium was shown to cause emphysema and reduce pulmonary function in male rats; the effect was less severe or delayed in onset if dietary zinc concentration was high. Interference with copper and iron metabolism was shown to occur in rats given low levels of cadmium orally. Depression of copper and iron metabolism of the rat fetus was found to occur when dams received very low doses of cadmium during gestation, even though very little cadmium passed the placental barrier.

A number of reports and reviews (*1–3*) have appeared indicating that interactions between essential nutrients and cadmium occur during exposure of experimental animals to compounds of this metal which significantly affect its toxicity. Among the essential nutrients which have been studied for possible interaction, there is convincing evidence that this occurs between cadmium and the dietary intake or metabolism of zinc, copper, and iron (*4–6*). When cadmium compounds are administered by inhalation or by oral ingestion, the two usual routes of human exposure, the mechanism of their toxicity may not be well understood; but it has become evident that among the metabolic targets of cadmium are processes and enzymes which require zinc, copper, or iron for their function, integrity, or stability.

In this presentation we shall discuss some recent experimental results which strongly indicate that in part the oral toxicity of cadmium compounds, especially when administered in low doses, may reside in disturbances of the metabolism of zinc, copper, and iron. This has been found to be the case when the dietary intakes of these essential metals were optimal or even excessive according to accepted dietary standards.

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Effects of Cadmium on Zinc Metabolism

Evidence for an interaction between cadmium and zinc nutrition or metabolism causing or altering toxicity has been presented by Parizek (*7*), Gunn et al. (*8–10*), Hill et al. (*11*), Bunn and Matrone (*12*), and Sporn et al. (*13*). Petering et al. (*14*), and Petering (*15*) found that low oral doses of cadmium chloride had adverse biological effects in rats when the dietary intake of zinc was low but had no such adverse effects when the dietary level of zinc was raised. Since these reports, we have ascertained that a number of biological effects of oral cadmium ingestion by rats other than growth retardation or depression of hemopoiesis reflect the interaction of zinc and cadmium, several of which will be described here.

Effect of Cadmium on Zinc Metabolism in the Liver

Recently El-gazzar et al. (*16*) pointed out that when 4.3 μg Cd/ml of drinking water was given chronically to male or female rats fed a good commercial diet, a marked alteration of the zinc bound to liver cytosol proteins occurred without any extensive induction of cadmium thionein. In addition, these investigators found that increasing the oral

Table 1. Dose effect of oral cadmium on female rat liver zinc and cadmium content.[a]

| | Cd, μg/ml in drinking water | Zn, μg/g dry weight | | | Cd, μg/g dry weight | | |
n		Whole liver homogenate	Cytosol	Total particulate matter	Whole liver homogenate	Cytosol	Total particulate matter
3	0	87.0	40.0	47.0	—	—	—
1	4.3	88.0	47.5	40.5	11.0	8.4	2.6
1	8.6	100.0	68.0	32.0	20.0	16.4	3.6
2	34.4	153.0	84.9	68.1	102.0	80.1	22.0

[a] Female weaning Sprague-Dawley rats were fed a commercial diet ad libitum with more than 60 ppm zinc for 200 days at which time they were sacrificed. The livers were removed quickly and kept at $-4°C$ until processed, at which time an aliquot was taken for analysis. The remainder of the homogenate was centrifuged at 105,000 g for 1 hr. Analyses were made of the homogenate and first cytosol. Zn and Cd values of the particulate fraction were calculated from these analyses. Calculated from data obtained by El-gazzar et al. (16).

dose of cadmium to 8.6 μg/ml caused even further alteration in the normal zinc-bound protein profiles of the liver cytosols as well as the formation of a distinct metallothionein protein fraction containing both cadmium and zinc.

These results are further emphasized in the data shown in Table 1, which have been derived from the findings of El-gazzar et al. (16). In Table 1 the response of zinc and cadmium concentrations in liver to the oral dose of cadmium is presented. These data demonstrate that there not only was an increase in the cytosolic concentration of zinc in relation to dose of cadmium, but that there were also unusual changes in the zinc content of the particulate fractions, changes which we believe may be related to or involved in the toxic action of cadmium. Furthermore, El-gazzar et al. (16) found that less than one-half of the liver cytosolic zinc at any given level of cadmium ingestion was associated with the metallothionein fraction.

These results indicate that even when the dietary intake of zinc is high, low levels of oral cadmium can greatly disturb normal zinc metabolism in the liver of the rat. Additionally, it should be noted that 32–45% of the liver zinc was found in the particulate fraction, regardless of the amount of cadmium administered or present in this organ. These results and the fact that 20% of the liver cadmium was found in the particulate fractions emphasize that more attention must be given to the effects of cadmium on cellular organelles in elucidating the mechanism of cadmium toxicity. This suggestion is in harmony with the report of Webb (17) that cadmium binds readily to nucleic acids, membranes, and proteins in general.

Effect of Cadmium and Zinc Interaction on the Lung

As was indicated above for effects of cadmium on liver, there is good evidence for considering the interaction of cadmium and zinc metabolism in

evaluating cadmium toxicity. Similarly, we have found that oral ingestion of cadmium at relatively low doses over long periods of time in rats leads to the development of centrilobular emphysema in the lungs. In addition, the pulmonary function of these rats was markedly reduced, indicating that the early morphologic lung lesions are closely associated with important physiologic pulmonary changes.

The effects of oral administration of 17.2 μg Cd/ml of drinking water on the morphology of the lungs of male rats receiving a good semipurified diet containing either 10 ppm or 40 ppm of zinc are demonstrated in Figures 1 and 2. In Figure 1a we see the histology of the lung of a rat receiving no cadmium but only the semipurified diet containing 10 ppm zinc. It may be noted that there is normal lung structure of the alveolar spaces and the respiratory bronchioles. In Figure 1b marked increases in the alveolar spaces and dilatation of the respiratory bronchioles are present in the lung of a rat receiving the same diet with 10 ppm zinc but also 17.2 μg Cd/ml drinking water. The cadmium was given during the last eight months of the experiment, which itself was of 11 months duration. Thus these findings, which are similar to those found in many other experiments, show that chronic administration of oral cadmium to rats on a diet with optimal zinc results in lung pathology.

In Figure 2a the histology of the lung of a rat receiving the same basic diet but with 40 ppm zinc is shown. Here again, as in Figure 1a, we find that the morphology of the alveolar spaces and respiratory bronchioles is within the normal limits. In Figure 2b we see the histology of the lung of a rat receiving the diet with 40 ppm zinc and in addition 17.2 μg Cd/ml in the drinking water. All other experimental conditions were the same as that for the rat described for Figure 1b. In this case (Fig. 2b), there was little loss of alveolar tissue. The respiratory bronchioles also were much less dilated than they were in the lung of the rat shown in Figure 1b.

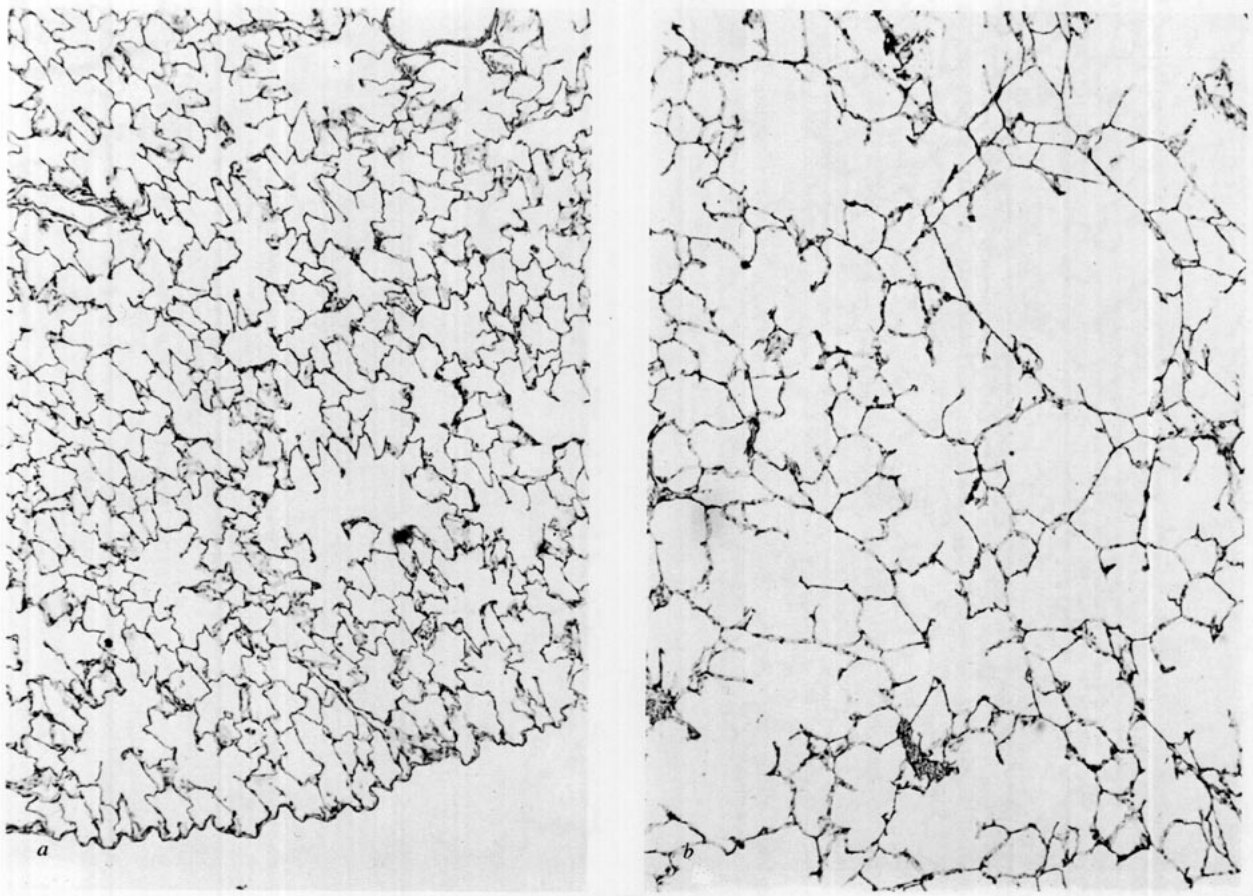The loss of alveolar tissue and the dilation of res-

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FIGURE 1. Lungs of rats maintained for 11 months on (*a*) a semi-purified diet and intake of 10 ppm zinc in the drinking water and (*b*) same diet but additionally, 17.2 ppm cadmium in the water for 8 months. The respiratory bronchioli and the alveolar structures in (*a*) are within normal limits. Notice the marked centrilobular and panacinar emphysema in (*b*) with loss of alveolar tissue. H & E stain, original magnifications 50 ×.

piratory bronchioles are marks of centrilobular emphysema. Since the absolute magnifications in Figures 1 and 2 are identical, we can conclude that the presence of excessive dietary zinc over that required for growth was associated with less lung pathology and probably with a slower development of the emphysematous lesions. Thus dietary zinc had a protective role in preventing this toxic effect of cadmium.

In a similar experiment for a shorter length of time, namely, four months, Lal (*18*) found similar but less severe pathology when he compared the effect of 17.2 μg Cd/ml drinking water on the lungs of male rats receiving either 5 ppm or 40 ppm zinc in a diet similar to that reported here. In fact, he found no lesions at all in the group getting 40 ppm of dietary zinc, but he did find early emphysematous lesions in the group receiving 5 ppm zinc. In Table 2 we have tabulated data taken from the report of Lal (*18*) in which are presented the concentrations of zinc and cadmium which he found in lungs, livers,

and kidneys from his groups of rats. These data show that only liver zinc and cadmium levels were significantly altered by changes in dietary zinc intake. In the lungs the zinc content was not altered, and the small change in cadmium due to differences in zinc intake was small, as were the absolute lung cadmium concentrations themselves. These data do not appear to indicate a direct relationship of either zinc or cadmium in the lung with the severity of the lung pathology.

In recent experiments we have been able to obtain certain pulmonary function measurements of isolated lungs from rats which had received oral cadmium. The changes in pulmonary function have at the same time been compared with lung pathology and these parameters have been found to be in good agreement. Vinegar and Choudhury (*19*) reported a significant increase in static compliance in the isolated lungs of male and female rats which had received 34.4 μg Cd/ml drinking water and a good commercial diet containing 60 ppm zinc for 520
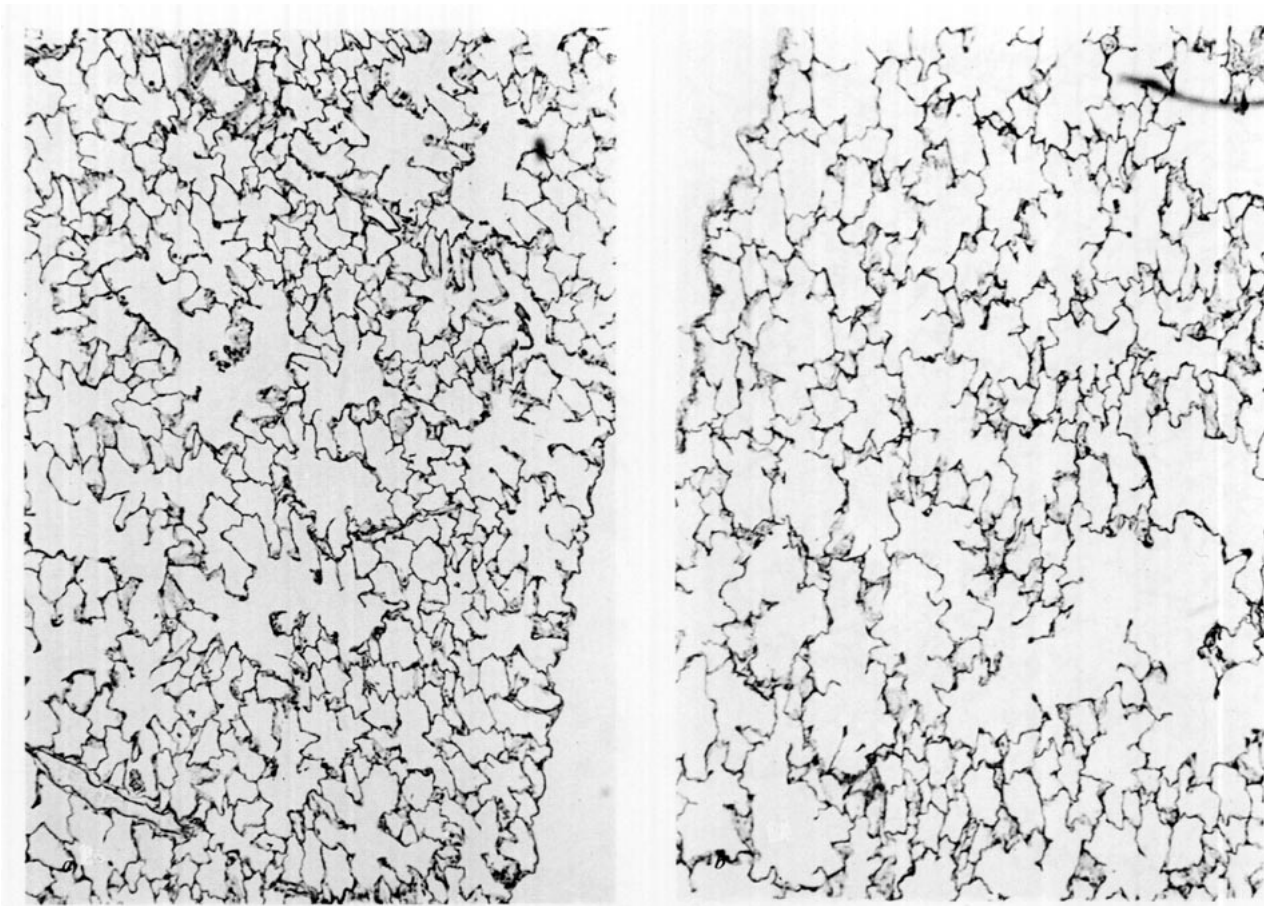
FIGURE 2. Lungs of rats fed (a) a controlled semipurified diet and 40 ppm of zinc in the drinking water for 11 months; (b) the same basic treatment as in Fig. 2a, but receiving for 8 months 17.2 ppm of cadmium, in the drinking water. Essentially, normal lung shown in (a), but in (b) both the respiratory bronchioli and many of the alveolar spaces are dilated. There is some loss of alveolar tissue. Slight to moderate centrilobular emphysema. H & E stain, original magnifications 50×.

Table 2. Zinc and cadmium content of lung, liver, and kidney of male rats receiving cadmium (17.2 μg/ml) orally.[a]

Dietary Zn	Zinc, μg/g dry weight			Cadmium, μg/g dry weight		
	Lung	Liver	Kidney	Lung	Liver	Kidney
5 μg/ml in drinking water	60.5	58.5	66.1	0.0	0.0	0.0
5 μg/ml in drinking water + Cd	67.9	13.4	93.1	1.52	18.0	72.6
40 μg/ml in drinking water	64.3	99.2	90.7	0.0	0.0	0.0
40 μg/ml in drinking water + Cd	74.6	91.6	77.5	1.02	2.1	29.8

[a] Male weanling Sprague-Dawley rats were fed ad libitum a good semipurified diet containing 20% dried egg white, 60% corn starch, 10% corn oil, 3% cellulose powder, and adequate vitamins and minerals except zinc. Zinc acetate was given in the distilled drinking water at levels of 5 or 40 μg/ml of water. At 120 days the rats were sacrificed, exsanguinated, and weighed portions of the lungs, liver, and kidneys were pooled, frozen, and used for analyses. Data taken from the report of Lal (18).

days. The males in this experiment also showed an increase in dynamic compliance from 1.276 to 2.212 cm³ water/kg. All of the rats had severe pulmonary emphysema.

Additional data obtained by Vinegar, Stemmer, and Choudhury (20) in our laboratory showed that male rats given 17.2 μg Cd/ml drinking water for 200 days had similar but less severe pulmonary function changes and exhibited less lung pathology. In recent experiments with the assistance of Vinegar we have

attempted to determine the lowest dose of cadmium which will produce lung lesions and alter pulmonary function. In these experiments it was found that 4.3 μg Cd/ml of water given for 200 days to rats receiving a commercial diet containing more than 60 ppm zinc did not produce either lung lesions or changes in static compliance. On the other hand, 8.6 μg Cd/ml water given for the same length of time did cause changes in pulmonary function and produced lung lesions. The results of the pulmonary function measurements are depicted in Figure 3. These data show that there was no difference in specific static compliance between the control and the 4.3 μg Cd/ml groups. There was however a significant increase in this parameter over control values for the 8.6 μg Cd/ml groups. Thus, again, there is evidence that by both morphologic changes or physiologic changes oral cadmium can be toxic to the lung.

These results taken as a whole show that ingestion of cadmium can cause the development of centrilobular emphysema in rats in a dose-related manner, and that the onset of the lesions is dependent on the length of time of the exposure and on the level of dietary zinc intake. On the other hand, the onset and severity of the lesions do not seem to be directly related to the cadmium burden of the lung,
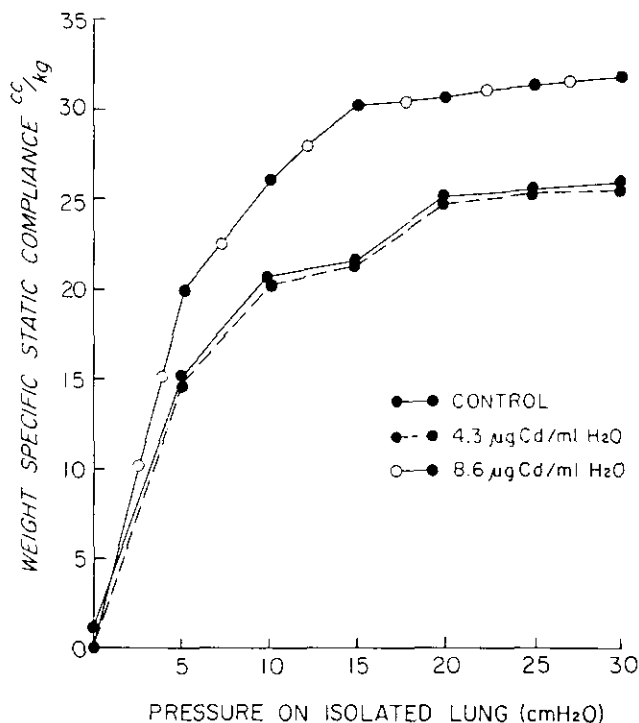

FIGURE 3. Weight-specific static compliance curves of lungs isolated at sacrifice from male rats fed a good commercial diet for 200 days after weaning and given the indicated levels of cadmium as CdCl₂ in the distilled drinking water.

nor to changes in concentration of zinc in the lung. These lesions occur in the absence of inflammation or evidence of infection. Therefore, it would seem that systemic humoral changes may occur during cadmium ingestion which result in emphysema, changes which may be inversely related to the amount of zinc taken in the diet. In this regard it is of interest to note that Cornicelli (21) found that there was, in fact, a significant reduction in serum antitryptic activity in rats exposed either orally or by inhalation to cadmium compounds, whereas there was no effect of Cd^{2+} added to serum on in vitro antitryptic activity.

Effect of Cadmium on Copper Metabolism and Iron Metabolism

Iron metabolism and copper metabolism are closely interrelated, and the effect of cadmium on one may easily involve interaction with the other. Therefore, these interactions will be discussed together.

Several recent reports from our laboratory (14, 15, 22) have shown that oral absorption of cadmium at moderately low concentrations in the drinking water of rats resulted in alterations of the concentrations of copper and iron in serum and kidneys, even when the diets contained high levels of these essential metals. In one of these reports, Murthy et al. (22) found that kidney levels of copper varied directly with the concentration of cadmium in the drinking water. Copper liver levels showed no such variation; only zinc showed a direct response to the cadmium ingested. Furthermore, these effects of cadmium on copper and zinc metabolism were always greater in the female rats than they were in the male rats, and cadmium accumulated to a greater extent in the visceral organs of females than in males. Thus, when the level of cadmium ingestion was 17.2 μg/ml of water, the concentrations in the liver of males of Zn:Cu:Cd found by Murthy et al. (22) were 114:13.3:20.4 while for the females it was 144: 19.5:39.4 μg/g dry weight. Similar values for kidney were for males 121:35.5:83.3 and for females 148:114.8:163.9 μg/g dry weight.

In a series of experiments designed to examine the effects on the fetuses and growing neonates of cadmium chloride administered orally to female rats before and/or during pregnancy, we found that serious alterations in copper and iron metabolism of the neonates occurred. This work was initiated after it was found that oral ingestion of cadmium chloride in the drinking water of pregnant rats up to 100 μg Cd/ml of drinking water did not produce any evidence of teratologic changes. In these experiments,

which are discussed below, we found that the fetus was a much more sensitive organism than its mother in regard to the impairment of copper and iron metabolism by oral cadmium.

In these experiments we fed adult female and also some males used in the breeding a well-fortified commercial stock diet during the entire period of investigation. The chow diet contained more than 60 ppm of zinc, more than 200 ppm of iron, 18 ppm of copper, and less than 3 ppm of cadmium. Cadmium chloride was given in the drinking water to the females before conception and or during the gestational period at levels of 0, 4.3, 8.6, and 17.2 μg Cd/ml for different periods of time. The animals were virgin Sprague-Dawley rats and were bred only once for the purposes of these experiments. The rats were housed in stainless steel cages, kept in a well-controlled environment, and fed the diets ad libitum. The results to be discussed involve those obtained when the females (a) received cadmium before and during gestation, (b) received cadmium before or during gestation, and (c) received cadmium in various concentrations before and during gestation.

Effect of Cadmium Given to Dams before and during Gestation

The first series of experiments was designed to investigate the effects that the length of time of exposure to cadmium before conception and during gestation may have had on the reproductive performance of the dam, on trace metal metabolism of the fetus, and finally on the growth and behavior of the neonate. The early studies of Cooper et al. (23) indicated that exposure of rat dams to moderately low oral doses of cadmium, though not teratologic in the accepted sense of the term, affected the behavior patterns of the grown neonates, and trace

metal metabolism of the new born pups was depressed.

In the first experiments the dams were given 17.2 μg Cd/ml of water for 60, 90, 120, and 150 days prior to conception and then in each case during the gestation period as well. The dams were allowed to deliver their young and then one-half of the litters were sacrificed for analytical studies and the other half of each litter was allowed to be suckled to weaning. The biochemical and physiological data from these experiments in which cadmium was given for 60 and 150 days prior to conception plus the gestation period are presented. These data are also representative of those found in the other two intermediate time periods, since length of exposure to cadmium prior to conception did not affect the results. There was no obvious interference with reproduction due to administration of cadmium. It was noted that in every experiment in this series the dams gained weight normally, delivered their young normally, and showed no significant increase in neonatal mortality over the controls.

The results shown in Table 3 demonstrate that the amount of cadmium transferred to the fetus was small, never being more than about 40% greater than that in the control fetuses, and the total amount always being less than 0.5 μg/g of dry weight. There was a consistent and significant lowering of whole body copper and iron in the pups, which seemed not be related to the length of time of cadmium administration. The reduction in copper in comparison with the controls was 33–40%, and for iron 25–40%. There was no significant alteration in whole body zinc of the pups.

Since the changes in copper metabolism and iron metabolism of the newborn pups were not influenced by the length of time used in the four experiments described here, it seemed evident that these serious alterations in biochemistry were related primarily to the exposure to cadmium of the dams

Table 3. Effect of dietary cadmium given before and during gestation on fetal viability and neonatal trace metal metabolism.

Group	No. pups born/stillborn	Live birth weight, g $\pm$ SE	Metal concentrations of whole pups, μg/g dry wt $\pm$ SE			
			Zn	Cu	Fe	Cd
	Cadmium given 60 days before and 21 days during gestation[a]					
Control	18/2	7.2 $\pm$ 0.1	155 $\pm$ 6	19.2 $\pm$ 1.3	371 $\pm$ 25	0.41 $\pm$ 0.02
17.2 μg Cd/ml in drinking water	23/2	6.6 $\pm$ 0.1[c]	143 $\pm$ 3	12.0 $\pm$ 0.6[c]	212 $\pm$ 8[d]	0.54 $\pm$ 0.04
	Cadmium given 150 days before and 21 days during gestation[b]					
Control	33/2	6.1 $\pm$ 0.1	118 $\pm$ 6	12.0 $\pm$ 1.2	303 $\pm$ 9	0.20 $\pm$ 0.03
17.2 μg Cd/ml in drinking water	40/6	6.3 $\pm$ 0.1	124 $\pm$ 4	8.0 $\pm$ 0.6[d]	232 $\pm$ 9[d]	0.28 $\pm$ 0.02

[a] The litters of two pregnant rats constituted each group. Purina laboratory chow was fed for the period indicated.

[b] The litters of three pregnant rats constituted each group. Purina laboratory chow was fed for the period indicated.

[c] Significantly different from controls at $p < 0.05$.

[d] Significantly different from controls at $p < 0.01$.

Table 4. Effect of dietary cadmium given before or during gestation on fetal viability and neonatal trace metal metabolism.

Group	No. pups born/stillborn	Live birth weight, g ± SE	Metal concentrations of whole pups, μg/g dry wt ± SE			
			Zn	Cu	Fe	Cd
Cadmium given 60 days prior to gestation only[a]						
Control	40/1	6.2 ± 0.1	118 ± 4	11.4 ± 0.7	389 ± 20	0.13 ± 0.00
17.2 μg Cd/ml in	45/19	6.1 ± 0.1	125 ± 5	9.9 ± 0.8	382 ± 10	0.14 ± 0.01
Cadmium given 21 days during gestation only[b]						
Control	21/0	6.8 ± 0.1	116 ± 4	9.4 ± 0.4	330 ± 6	0.46 ± 0.05
17.2 μg Cd/ml in	22/9	6.4 ± 0.1[c]	104 ± 3[c]	5.7 ± 0.4[d]	267 ± 17[d]	0.48 ± 0.00

[a] Litters of three pregnant rats constituted each group. Purina laboratory chow was fed to all dams.

[b] Litters of two pregnant rats constituted each group. Purina laboratory chow was fed to all dams.

[c] Significantly different from controls at $p < 0.05$.

[d] Significantly different from controls at $p < 0.01$.

during gestation, which was common to each experiment. We therefore turned our attention next to explicitly examining the effects of cadmium administration only prior to conception or only during gestation.

Effect on Neonates of Cadmium Given to Dams prior to or during Gestation

The data presented in Table 4 are for female rats exposed to 17.2 μg Cd/ml of water only prior to conception or only during gestation. The same general protocol was used as described above. These data conclusively show that a significant reduction in pup whole body concentrations of copper and iron was found only when cadmium was given for only 21 days during gestation. There was also a significant but smaller decrease in whole body zinc in the pups of these mothers, which had not occurred previously in our experience. The large number of dead pups, which occurred in both sections of this experimental series, cannot be explained but also cannot be attributed to the variations in the experimental design.

On the other hand, this experiment shows that cadmium given only during the period before conception had no effect on the trace metal metabolism of the pups. It is of interest that there was no significant increase in whole body cadmium concentrations of the pups in either experiment A or B. Again, the mothers in all of the groups shown in Table 3 had a normal gestation period and experienced no obvious difficulty with delivery. Cooper et al. (23) have reported that a reduction of spontaneous locomotor activity (SLA) of the grown neonates of this experiment was found only in the group which had been born of dams receiving cadmium during gestation only. Thus it seems evident that the burden of cadmium alone of the dams did not affect the neonates or fetuses, but exposure during pregnancy was the hazard to the fetus and neonates.

Response of Neonates to Varying Dosage of Cadmium Ingested by Dams

With these data it seemed that it was opportune to explore the effects of dosage of oral cadmium given to the dams on the trace metal metabolism as well as behavioral changes of the pups and neonates. In order to investigate the dose-response relationships we carried out the two experiments described in Table 5. In experiment A, 4.3 or 8.6 μg Cd/ml of drinking water was administered to the dams for 90 days prior to conception and also during gestation. In experiment B, 17.2 or 34.4 μg Cd/ml of water was given for the same length of time. All other experimental conditions were the same as for the previous experiments cited above.

The data presented in Table 5 show that there were no significant differences in any groups with respect to reproductive capacity, and a significant reduction in birth weight only in experiment B, where the highest levels of cadmium were involved. Whole body zinc levels of the pups were not affected in this series of groups by any dose of cadmium. There was, however, a reduction in pup body iron in every group administered cadmium except the one receiving 4.3 μg Cd/ml, the lowest level and there was a significant reduction in pup body copper in every group of which the mothers received cadmium. The reduction in iron of the pups appeared to be dose-related to the cadmium ingested by the dams, but this was not true of the reduction in copper. Thus the no-effect level for changes in iron metabolism due to cadmium ingestion by the dam was 4.3 μg Cd/ml of water, but at this level there was still a marked disturbance of copper metabolism. In this regard it is of interest to note that Cooper et al. (23) have reported that SLA of the neonates at 6–10 weeks of age was significantly reduced in those whose mothers had received 4.3, 8.6, and 17.2 μg Cd/ml and significantly increased in the group whose mothers had received

Table 5. Dose effect of dietary cadmium given before and during gestation on fetal viability and neonatal trace metal metabolism.[a]

	No. pups born/still born	Live birth weight, g ± SE	Metal concentrations of whole pups, μg/g dry wt ± SE			
			Zn	Cu	Fe	Cd
Control	54/0	6.3 ± 0.2	127 ± 3	15.0 ± 0.7	417 ± 15	0.43 ± 0.01
4.3 μg Cd/ml in drinking water	55/0	6.1 ± 0.2	137 ± 3	11.0 ± 0.4[b]	359 ± 14	0.47 ± 0.01
8.6 μg Cd/ml in drinking water	52/0	6.2 ± 0.1	137 ± 3	12.0 ± 0.8[c]	336 ± 9[b]	0.49 ± 0.01
Control	41/0	6.7 ± 0.1	132 ± 4	12.0 ± 0.8	421 ± 19	0.21 ± 0.01
17.2 μg Cd/ml in drinking water	47/1	6.0 ± 0.1[b]	131 ± 2	9.0 ± 0.4[b]	346 ± 14[b]	0.21 ± 0.01
34.4 μg Cd/ml in drinking water	59/1	6.0 ± 0.1[b]	130 ± 2	8.0 ± 0.3[b]	224 ± 8[b]	0.24 ± 0.01

[a] Purina laboratory chow was fed to all adult females. Litters from five pregnant females constituted each group.
[b] Significantly different from controls at $p < 0.01$.
[c] Significantly different from controls at $p < 0.05$.

34.4 μg Cd/ml of water. It would then appear that the reduction in SLA behavior of the growing neonates is more closely associated with the newborn deficit in copper than with any other metabolic change thus far measured. Since copper metabolism and iron metabolism are intimately associated in hematopoiesis and in the processes for synthesis of other heme-iron compounds, it may be that the low copper, together with the tendency for lowered iron in the 4.3 μg Cd/ml water group, is significantly linked in the processes underlying the behavioral deficits found by Cooper et al. (23). Regardless of the lack of a definite mechanism for the behavioral changes observed, it is evident that oral ingestion of cadmium during gestation by female rats leads to pronounced alterations in copper and or iron metabolism when there is no obvious toxicity to the dam and when the level of cadmium is very low.

Discussion and Comment

The data presented here show that oral ingestion of cadmium even at relatively low doses can under certain dietary and physiological conditions markedly disturb zinc, copper, and iron metabolism, even when the diets are well-fortified with these essential metals. The finding by El-gazzar et al. (16) that ingestion of very low levels of cadmium can disturb the zinc metabolism in the livers of rats without the formation of appreciable amounts of either cadmium or zinc metallothioneins is of great importance. It raises serious questions about the significance of the induction of cadmium metallothionein during long-term and low-level environmental exposure as being either a protective or toxic component of the chronic health effects of cadmium. Their experiments, rather, suggest that the disturbance of zinc metabolism needs more

evaluation as a causative factor in the chronic health effects of cadmium.

The experiments cited here which show that chronic ingestion of oral cadmium chloride by rats leads to lung pathology indicative of centrilobular emphysema and to decreased pulmonary function is the first time to our knowledge that oral cadmium has been implicated in this kind of pathology. These data suggest that chronic exposure to oral cadmium together with other causative factors may be involved in the wide-spread incidence of emphysema in this country. In this regard it is of interest to recall that tobacco smoke contains appreciable levels of cadmium (24) which together with other irritants in the smoke may be of importance in affecting the pulmonary function of both smokers and non-smokers. The results presented here certainly indicate that we should be concerned not only with the direct effects of cadmium on the lung when it is inhaled in large amounts in certain workplaces, but also when it is taken into the system by any route over long periods of time. The data in this regard indicate that the effects of cadmium on the lung may be indirect and systemic rather than due to the cadmium burden of this organ.

Finally the importance of the finding that high levels of dietary zinc are protective with respect to the pulmonary effects of oral cadmium exposure cannot be overemphasized, since it is known that a large portion of our population is receiving less than the recommended daily allowance of dietary zinc. It further indicates that in a complex industrial society the dietary level of zinc and perhaps other nutrients cannot be determined solely on the basis of their growth effects for the young and for the needs of the child-bearing female, as has been the case in the past, but must be determined on the basis of environmental and occupational stresses as well.

Of great interest and significance is the fact that copper and iron metabolism is disturbed in the fetus and neonate by administering oral cadmium at low doses to the dams during pregnancy, and that the reductions in copper and iron metabolism are associated with behavioral changes in these offspring. Our data extend and provide a somewhat more sensitive measure of the effects of cadmium on the fetus described by Pond and Walker (25) and by Webster (26). Pond and Walker (25) used a very high level of oral cadmium—namely, 200 ppm in the diet—and the dietary levels of zinc, copper, or iron which they used could not be readily ascertained from the information given by them on their practical diet. They did, however, limit the intake of calcium in one group and found that the amounts of cadmium which passed the placental barrier were greatly increased when calcium was low. They found relatively large amounts of cadmium in the fetuses, which we did not. In addition, our diet always contained high levels of calcium and the rats in our experiments were given much smaller doses of cadmium than was given by Pond and Walker (25). These differences may account for the variations in the amounts of cadmium which passed the placental barrier.

Webster (26) used a commercial diet and mice for his experiments. He found that when cadmium in the drinking water was at levels of 20 or 40 μg/ml the fetal weights were reduced, and anemia appeared in both dams and fetuses. The anemia of the dams responded to the administration of iron dextran and so was considered an iron deficiency anemia. This author gave no information on the iron, copper, or cadmium content of the fetuses, and so we cannot fully evaluate his data in comparison with ours. We did not find anemia in the dams; otherwise, we believe that our data and those of Webster are essentially in agreement.

In another paper, Pollitt and Leibel (27) pointed out that iron deficiency anemia in young children can cause behavioral deficits. Our data and those of Cooper et al. (23) certainly underscore the necessity for studying much more intensively the relationships of trace metal biochemistry and nutrition to the problems associated with behavioral deficits in the young.

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