Archives of Environmental Health: An International Journal
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/vzeh20

Studies of Zinc Metabolism in the Rat

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Published online: 22 Apr 2013.

To cite this article: Harold G. Petering PhD , Melvin A. Johnson PhD & Klaus L. Stemmer MD (1971) Studies of Zinc Metabolism in the Rat, Archives of Environmental Health: An International Journal, 23:2, 93-101, DOI: 10.1080/00039896.1971.10665962

To link to this article: http://dx.doi.org/10.1080/00039896.1971.10665962

Scientific Communications

Studies of Zinc Metabolism in the Rat

I. Dose-Response Effects of Cadmium

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Nutritional zinc can be studied in the male rat as a pharmacologic agent. Responses to zinc in respect to body growth, hematologic effects, blood and tissue levels, and body temperature control are all log-dose related. Copper levels in liver and kidney are influenced by zinc intake. Cadmium alters these responses inversely in relation to the zinc intake, and thus can be considered as an antimetabolite of zinc. Cadmium was localized in liver and kidney but not in testes of our animals. Our data indicate that there is very minimal storage of readily available zinc in the male rat.

MANY recent reports and reviews have adequately indicated the importance of zinc as an essential element for man, for animals, and for lower organisms.[1-3] In addition, it has been shown that zinc is specifically useful in promoting wound healing and reducing effects of vascular impairment in man.[4,5] Petering et al,[6] in a study that indicated that zinc is required for transplanted tumor growth in rodents, also showed that an antitumor drug could reduce the efficacy of zinc in a nutritionally adequate diet.

These facts have led us to consider the effects of environmental agents on zinc metabolism and to try to assess the importance of inadequate nutritional intake of zinc in relation to environmental exposure to a low level of cadmium, a preliminary report of which has been presented elsewhere.[7] We wish to report here experiments which show the dose-response relationships to zinc acetate administered in the drinking water of rats and the effect of cadmium on these normal responses.

Submitted for publication Dec 10, 1970; accepted April 1, 1971.

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Experimental Methods

In the studies reported here we used weanling male Sprague-Dawley rats (50 to 60 gm) divided into the designated groups and housed individually in stainless steel wire cages. All of the rats were fed the same semipurified diet ad libitum, the composition of which is given in Table 1. The diet contained less than 2μg of zinc per gram and an excess of biotin to avoid the possible effects of avidin.

The zinc and cadmium supplements were given in the drinking water according to the experimental design shown in Table 2. Groups 1a, 2a, 3a, and 4a initially contained 20, 15, 15, and 10 rats, respectively, and were given the amount of zinc indicated in Table 2. On day 28, five rats were removed from each of groups 1a, 2a, and 3a to form groups 1b, 2b, and 3b, which were given the supplements of zinc and cadmium indicated in Table 2 for the b groups. On day 53, five rats were separated from group 4a to form group 4b and these received only deionized water in place of the zinc-supplemented water for the remainder of the experiment. Thus, we were able to study the dose-response relationships of zinc and the effect of giving cadmium in zinc-cadmium ratios of 1:1 and 4:1 in groups 2b and 3b, respectively. In addition, we obtained information on the reversibility of the zinc deficiency (group 1b) and the zinc sufficiency (excess) (group 4b).

The zinc, copper, and cadmium analyses were determined by atomic absorption spectrophotometry on dry-ashed samples of wet tissue and wet-ashed samples of serum, determinations being made on pooled samples from each group. The values for the samples were calculated by comparison with known analytical standards of zinc chloride, cupric chloride, and cadmium chloride.

Groups 1a and 1b were killed on day 56 because of the poor condition of animals in group 1a. Groups 2a and 2b were killed on day

Table 1.—*Composition of Diet*

Ingredients	%	Zn Content (ppm)
Corn starch	68	1.1
Egg white (dried)	20	5.4
Crude soybean oil	5	...
Cellulose flour	3	...
Salts "W"*	4	4.9
Fat-soluble vitamins† (in crude soybean oil)	...	...
Water-soluble vitamins‡ (in corn starch)	...	...

* Wesson modification of Osborn-Mendel salt mix: $CaCo_3$, 21.00%; $Ca_3(PO_4)_2$, 14.90%; $CuSo_4 \cdot 5H_2O$, 0.039%; $Fe\ PO_4 \cdot 4H_2O$, 1.47%; $MgSo_4$, 9.00%; $MnSo_4$, 0.02%; $K_2Al_2(So_4)_4 \cdot 24H_2O$, 0.009%; KCl, 12.00%; KI, 0.005%, KH_2PO_4, 31%; NaCl, 10.50%; NaF, 0.057%.

† Fat-soluble vitamins per 100 gm: 3,000 international units (IU) of vitamin A, 400 IU of vitamin D3, 40 mg of mixed tocopherols, and 200μg of vitamin K3.

‡ Water-soluble vitamins per 100 gm: 40 mg inositol, 100 mg choline chloride, 2 mg thiamine hydrochloride, 1 mg pyridoxine hydrochloride, 6 mg calcium pantothenate, 10 mg niacinamide, 2μg riboflavin, 20μg biotin, 50μg folic acid, and 2μg vitamin B12.

Table 2.—*Design of Experiment: Supplements in Drinking Water*

a Groups	Initial No. of Rats	b Groups*
1: No Zn day 0-56	20	(+) 30.5μM Zn $(AcO)_2$ (day 28-56)
2: 30.5μM Zn $(AcO)_2$ (day 0-74)	15	(+) 30.5μM $CdCl_2$ (day 28-74)
3: 122.0μM Zn $(AcO)_2$ (day 0-78)	15	(+) 30.5μM $CdCl_2$ (day 28-78)
4: 488μM Zn $(AcO)_2$ (day 0-78)	10	(—) Zn $(AcO)_2$ (day 53-78)

*(+), added to previous supplement; (—), omitted from previous supplement.

74 and groups 3a, 3b, 4a, and 4b were killed on day 78.

Results

Growth.—The data shown in Fig 1 reveal that we had reached the optimum level of zinc for growth with 122μM $Zn(OAc)_2$ drinking water since four times this concentration had no real effect on body weight of the rats (of group 3a vs 4a). They also show that 30.5μM zinc gave an intermediate response (group 2a) and that the basal dietary regimen including deionized water constituted a ration very deficient in zinc.

When these growth curves are compared with those in Fig 2, we see that the initial growth rates of groups 1b, 2b, 3b, and 4b compared favorably with those of groups 1a, 2a, 3a, and 4a. However, when cadmium was added to the drinking water of group 2b at a ratio of one part zinc to one part cadmium from day 28, there was a slowing of the growth rate which was easily noticeable after day 49. On the other hand, there was no effect on growth on adding cadmium to the diet of group 3b on day 28 in the ratio of four parts zinc to one part cadmium.

Addition of the low level of 30.5μM of zinc to the diet of group 1b on day 28 caused an immediate increase in the growth rate, indicating the rapidity with which zinc deficiency symptoms can be reversed, which is similar to the response reported by Swenerton and Hurley.[8] Similarly, the rapid reduction of growth in group 4b after day 53 indicates the rapidity with which zinc deficiency can be induced in large, growing rats receiving excessive zinc. These data suggest that the zinc needs of the rat must be met from daily dietary intake and that there is no extensive storage of zinc.

Pathologic Findings.—At the same time that there was evidence in the growth rate of our rats of the dose response to zinc intake and similar effects due to interaction with cadmium when the zinc-cadmium ratio was 1:1, we also found gross pathologic evidence of these responses. Thus, group 1a, which was the deficient group, exhibited marked alopecia and edematous skin lesions with erythematosis about the mouth and on the feet (Fig 3). The tails of some of the deficient rats were scaly, and other rats exhibited skin lesions around the eyes. There was evidence of inhibition of bony development, especially in the epiphyseal areas.

We found a loss of sebaceous glands and hair follicles, and a loss of capillaries in the skin. There was marked hyperkeratosis of the forestomach and keratinization of the cornea of the eye of the zinc-deficient animals. Rats receiving cadmium in group 2b showed a marked keratinization of the cornea similar to the zinc-deficient rats in addition to the reduction in growth rate. We could find no pathological signs of any significance in the gonads of animals from any groups.

There was a definite effect of zinc nutriture on the hematologic picture which was dose-related. The data of Fig 4 and 5 obtained on day 53 (groups 1a, 2a, 3a, and 4a) indicate that as the zinc intake increased, the white blood cell count (WBC) dropped from 19.3×10^3 to 15.7×10^3 and the granulocyte count dropped from 3,667 to 1,300,

while there was a tendency of the lymphocyte count to rise from 76.7% to 87.3%. In the same groups of animals, the hematocrit (packed cell volume) decreased from 54.3% to 47.7% and the hemoglobin values were diminished from 17.7 gm/100 ml to 14.4 gm/100 ml. The very regular inverse relationship of hematologic response to zinc is a curious observation and may well relate to the reported modification of copper and iron effects by zinc.[9]

Blood Levels of Zinc, Copper, and Cadmium.—Our data for the zinc, copper, and cadmium content of whole blood are presented in Table 3. These results show, first, that the zinc content is directly related to zinc intake, with the highest level in group 4a being much higher than that of group 3a, although the growth rate of these two groups was identical; second, that the copper content of whole blood was not increased above the value of 220μg/100 gm of group 2a, and thus only the deficient group (1a) was different, being lower (130μg/100 gm); and third, that cadmium in whole blood from animals not receiving this toxic element was very low and increased slightly as the zinc intake increased.

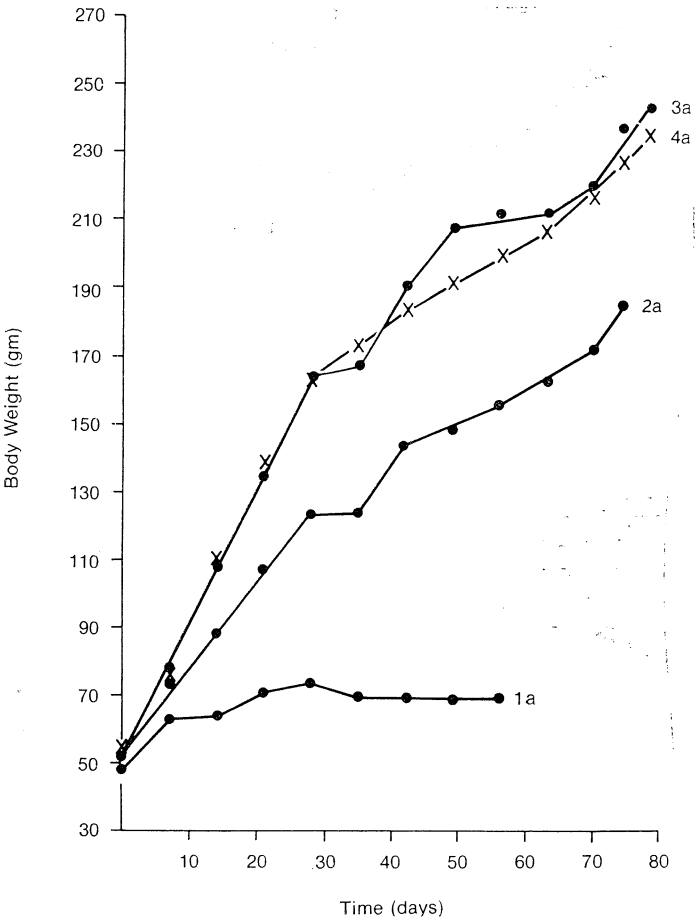

Fig 1.—Growth curves of male rats on zinc-deficient diet plus indicated zinc supplements in drinking water for entire experimental period. The supplements were as follows: group 1a, no zinc; group 2a, 30.5μM zinc; group 3a, 122.0μM zinc; and group 4a, 488μM zinc.

However, this picture was altered in the *b* groups where changes were made during the experiment. In group 1b there is an increase in zinc due to the added level of zinc in the water from day 28 to 54 when the blood was taken. Similarly, the value of copper for group 1b was higher than that for 1a, which is consistent with the response of the other groups (2a, 3a, and 4a) receiving zinc supplements from the beginning of the experiment. When zinc was removed from the diet of group 4b on day 53, cessation of growth ensued, with the appearance of gross skin lesions; and, this situation was paralleled by a drastic diminution in both the zinc (187μg/100 gm) and copper (127μg/100 gm) content of the blood.

When cadmium was given to group 2b in the ratio of one part zinc to one part cadmium, zinc and copper levels of blood greatly increased. This indicates either a mobilization of these metals from the tissue as the animals' growth rate was reduced or the unavailability of these bloodborne essential metals for vital functions owing to interference by cadmium. These observations are reinforced by examining the zinc and copper values due to cadmium intake in group 3b, when the zinc-cadmium ratio was 4:1. It should be remembered that group 3b did not

show a reduced growth rate or gross pathologic findings. The blood levels of zinc and copper of group 3b were also only slightly different from those of 3a, although the lower value of 400μg/100 gm for zinc in group 3b may truly reflect some alteration in the absorption of zinc due to cadmium absorption.

That cadmium was absorbed is shown by the elevated cadmium levels in blood of groups 2b and 3b, respectively, and by the tissue levels of cadmium given below. The elevated cadmium in the blood of group 4b (reduced intake of zinc) may be due to a mobilization of this element from tissue depots caused by the loss of weight in these rats.

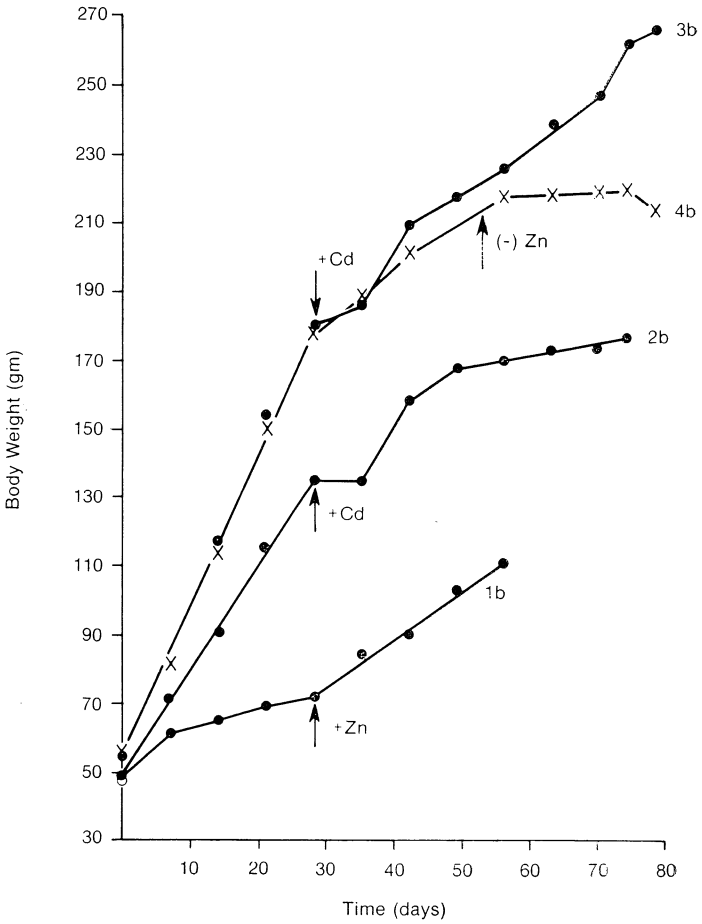

Fig 2.—Growth curves of male rats on zinc-deficient diet plus indicated initial supplements of zinc in drinking water and subsequent supplements of zinc and cadmium for each group. The initial supplements in drinking water were as follows: group 1b, no zinc; group 2b, 30.5μM zinc; group 3b, 122μM zinc; and group 4b, 488μM zinc. The subsequent supplements of zinc and cadmium were as follows: group 1b, 30.5μM zinc only from day 28; group 2b, 30.4μM cadmium from day 28; group 3b, 30.4μM cadmium from day 28; and group 4b, no zinc from day 53. **Plus** and **minus** signs indicate elements added or removed, respectively, from drinking water at the time indicated.

Tissue Levels of Zinc, Copper, and Cadmium.— The effects of varying the intake of zinc on the concentrations of zinc, copper, and cadmium in liver, kidney, and testes are given in Table 4. These data show a consistent fall in the zinc and copper concentration in liver tissue as the drinking water concentration was increased from 30.5μM to 488μM zinc (groups 2a, 3a, and 4a). In respect to the levels of these metals in the kidney, we found that the concentration of zinc rose markedly from 16.5μg to 24.9μg/gm and that of copper rose slightly from 6.9μg to 8.0μg/gm (groups 2a, 3a, and 4a) as the zinc intake was increased from 30.5μM to 488μM. With respect to cadmium, there seemed to be little variation in the very low levels in liver, but in kidney and testes the values in group 4a appeared to be elevated. The concentrations of zinc, copper, and cadmium in liver and kidney in group 1a were not entirely consistent with the values in the other *a* groups as indicated by lower level of zinc in liver and the higher copper level in kidney tissue. It must be remembered that this group did not grow appreciably and that the data were obtained on day 54, rather than at the later date for the other *a* groups.

Considering the effect of changing the regimens in the *b* groups, we have different but interesting results. When cadmium was added to the drinking water of groups 2b and 3b, there was no significant change in the zinc value of liver and kidney of group 2b, but there were distinct increases in the same tissues in group 3b. On the other hand,

the effect of cadmium greatly reduced the zinc value and raised the copper value of testes in group 2b, where the zinc-cadmium ratio was 1:1, but had very little effect on the related values of group 3b, where the zinc-cadmium ratio was 4:1. The great increase in cadmium in the liver and kidney of groups 2b and 3b in comparison with similar values of groups 2a and 3a certainly indicates that cadmium was well absorbed and localized in these tissues. The cadmium level of kidney was not affected by the nutritional intake of zinc but in liver it appears that cadmium was lower in group 3b, where the zinc-cadmium ratio was 4:1, than it was in group 2b, where the ratio was 1:1. Rather unexpectedly, we did not find any marked concentration of the orally administered cadmium in the testes of our rats.

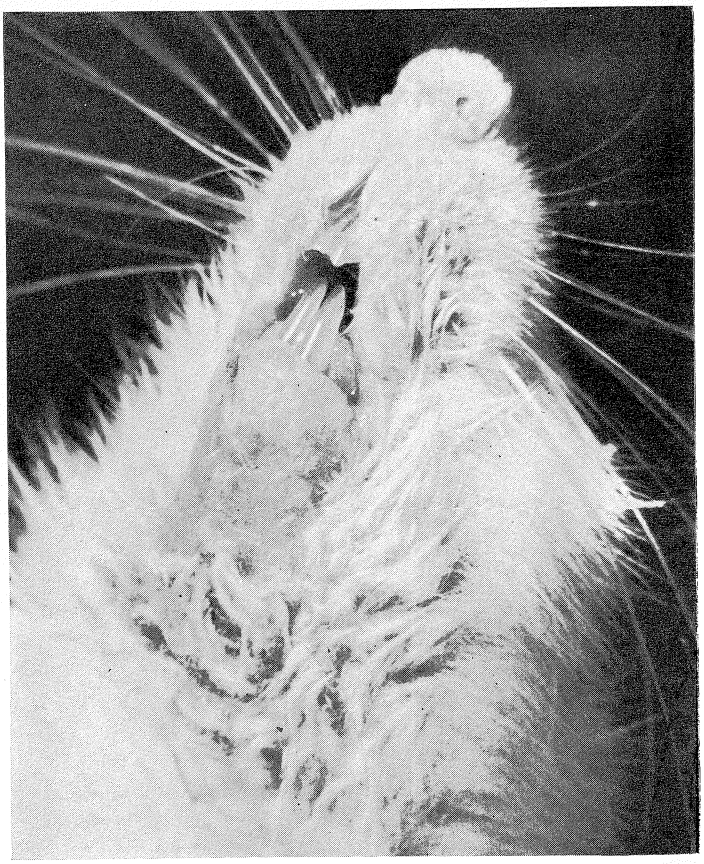

Fig 3.—Edematous condition of mouth of group 1a rat after seven weeks on zinc-deficient diet.

The removal of zinc from group 4b from day 53 to 78 resulted in an elevation of the liver zinc and copper, as well as an increase in kidney copper. Kidney zinc was not changed in group 4b. The liver shifts in zinc and copper are what one would expect in comparison with the data for lowered intake of zinc described above for groups 1a and 2a.

Body Temperature Changes.—Previously, one of us (H.G.P.) and J. A. Crim (unpublished data) had found that zinc deficiency or reduced zinc metabolism interfered with peripheral circulation. In the present experiment, it was found that rectal temperature was directly related to nutritional intake of zinc as is shown in Table 5. Here we have presented data taken on day 21 and 74. The data for day 21 involved only the changes in zinc intake and show that the level of zinc nutrition affects the body temperature.

In the data taken on day 74, just before the killing of the animals, we see that this relationship has become more acute for the animals in groups 2a, 3a, and 4a (group 1a and 1b were killed on day 55). Furthermore, the rats in groups 2b and 3b, which received cadmium from day 28 on, have rectal temperatures lower than rats in comparative groups 2a and 3a which received only zinc supplements in the drinking water. Thus, cadmium, which has been shown to affect growth adversely, to cause skin and eye lesions, and to alter the hematology and tissue metabolism of zinc and copper, now is shown to have another interesting physiological effect, namely, to alter the temperature regulatory mechanism of the rat through effect on the peripheral circulation.

The temperature of group 4b, which had received no zinc supplement from day 53, was lower than that of group 4a. Thus, the removal of zinc from a group of rats which were receiving an excess of zinc insofar as growth response was concerned, did show its effect on body temperature control.

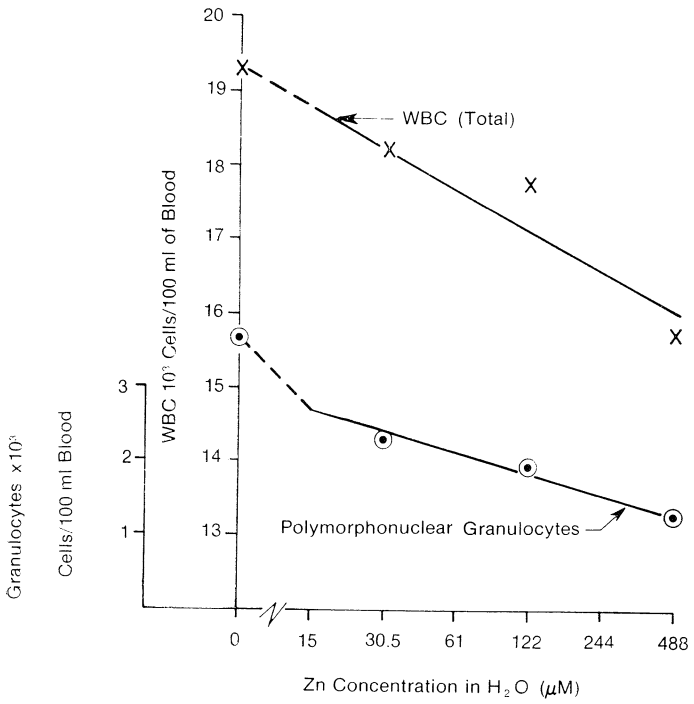

Fig 4.—Data showing dose response of WBC and granulocytes to zinc supplementation.

Comment

Our observations enlarge the horizon defined by the many studies on the essential nature of zinc in the metabolism of man and animals,[1,2,10,11] and add several important dimensions. They show that the response of the male rat to a wide range of oral intake of zinc, much below toxic levels, is graded, regular, and consistent. Thus, we have found no all-or-none phenomena in the metabolic activity of zinc and we believe that zinc metabolism can be studied best by using accepted methods of pharmacology.

These findings are important, for they suggest that there can be subclinical aspects of zinc nutrition. They also show that even an excess of zinc, insofar as growth is concerned, has physiological effects on hematology and temperature control.

The rapid onset of response to zinc administration or to its removal, as seen in groups 1b and 4b, suggests that there is no marked storage of this element. These rapid responses also show that the need for adequate nutritional intake of zinc is a daily one for the rat and that wide variations in daily intake may not average out well in respect to physiological response.

The experimental groups receiving cadmium (groups 2b and 3b) demonstrate that toxic symptoms in cadmium (growth reduction and gross pathology) are directly related to the zinc-cadmium ratio, indicating again that some of the toxicity of the cadmium must involve an interference with zinc metabolism, as Hill and Matrone[9] have reported. This is further indicated by the disturbance of the zinc and copper levels of kidney and liver of groups receiving cadmium (2b and 3b). A most interesting finding was the lack of any marked accumulation of cadmium in the testes due to oral ingestion of the element. Also of importance is the fact that cadmium altered the zinc and copper levels of testes in group 2b where the zinc-cadmium ratio was 1:1. The fact that cadmium showed effects only relative to the zinc intake adds to the importance of our finding that zinc response appears directly related to the log of the concentration in the drinking water, the sole source of dietary zinc.

The effect of zinc intake on rectal temperature confirms the earlier observation of one of us (H.G.P.). The body temperature of rats was not only related to the long-term nutritional intake but also sensitive to the removal of zinc from the diet of the growing rats of group 4b. This effect of zinc on body temperature may be related to the circulatory effects of zinc which have been described in patients with claudication by Pories et al.[4,5] Furthermore, the suggestion by Henzel et al[12] that these clinical effects of zinc, which they confirmed, are pharmacologic in nature is understandable in the light of our finding that the effect of zinc as a nutritional agent is always pharmacologic in its mechanism of action—ie, definitely log-dose-related and having various levels of activity.

These studies emphasize the need to recog-

nize the vulnerability of zinc metabolism to environmental factors, such as inadequate nutrition, sporadic nutritional variations of zinc, or the effect of environmental contaminants such as cadmium. It may well be that other environmental factors alter zinc metabolism as the basis of their action, for there are aspects of Raynaud's disease, atherosclerosis, arthritis, psoriasis, and hypertension which seem to be related to zinc deficiency or impaired zinc metabolism.

Our observations on the effect of zinc on body temperature and the adverse effect of cadmium in this regard, along with the observation that zinc-deficient rats had a loss of capillaries in the skin, could help to explain the interrelationship of cadmium and zinc in essential hypertension, as proposed by Schroeder.[13]

Although we were able to find the usual pathologic symptoms of zinc deficiency, namely alopecia, retarded growth, skin lesions, and the like, we were not able to find any effects either of zinc deficiency or cadmium ingestion on the gonads. This is remarkable in the light of the usual descriptions of pathology for both zinc deficiency and cadmium toxicity.

The absence of morphologic alterations in the testes is contrary to the findings of Gunn et al.[14-16] However, a comparison of their work with ours makes it apparent that they administered by parenteral injection about 30 times the daily amount of cadmium which we gave orally. Thus, Gunn and co-workers,[17,18] who demonstrated that the primary effect of parenterally administered cadmium chloride on the gonads was an extreme effect on the supporting blood vessels, were studying the acute toxicity of cadmium, whereas we studied chronic toxicity at low levels of cadmium.

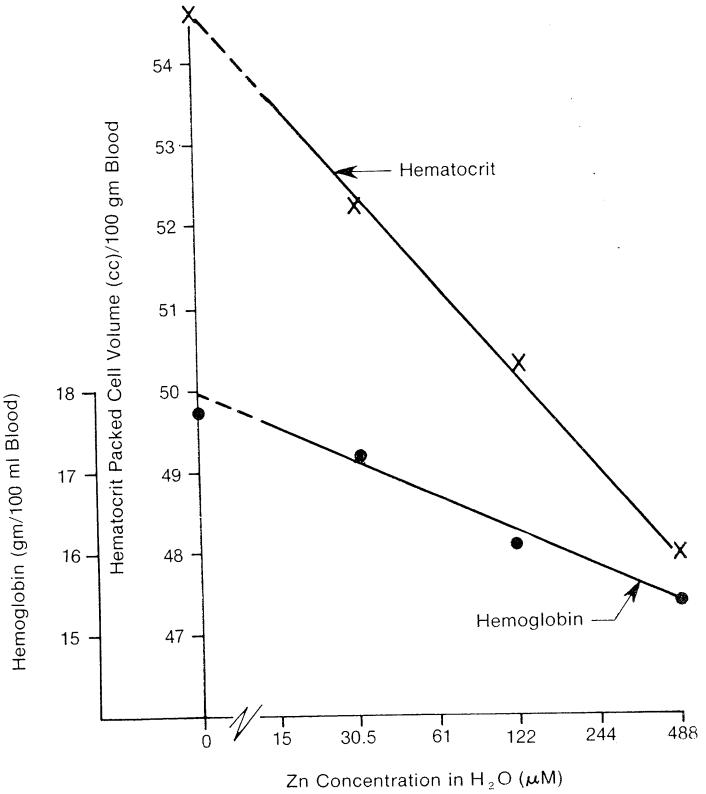

Fig 5.—Data showing dose response of red blood cells to zinc supplementation.

Table 3.—*Metal Concentration in Whole Blood*

Group	Day of Sample	Treatment*	Metal Concentration, μg/100 gm Zn	Cu	Cd
1a	54	No Zn^{2+}	380	130	3
1b	54	(+) Zn^{2+} 30.5μM (day 28-54)	480	164	3
2a	74	30.5μM Zn^{2+}	384	220	7
2b	74	30.5μM Zn^{2+} (+) Cd^{2+} 30.5μM (day 28-74)	800	355	18
3a	78	122μM Zn^{2+}	504	240	7
3b	78	122 (+) Cd^{2+} 30.5μM (day 28-78)	400	265	18
4a	78	488μM Zn^{2+}	900	230	8
4b	78	488μM Zn^{2+} (—) Zn^{2+} (day 53-78)	187	127	17

* (+), added to previous supplement; (—), omitted from previous supplement.

Table 4.—*Concentration of Zinc, Copper, and Cadmium in Tissues (μg/gm, Wet Weight)*

Group	Day of Sample	Treatment*	Liver			Kidney			Testes		
			Zn	Cu	Cd	Zn	Cu	Cd	Zn	Cu	Cd
1a	54	No Zn^{2+}	22.2	4.5	0.11	16.0	11.0	0.13	...	...	...
1b	54	No Zn^{2+} (+) Zn^{2+}, 30.5μM (day 28-54)	...	...	...	14.6	4.9	0.21	...	...	...
2a	74	30.5μM Zn^{2+}	29.9	3.3	0.06	16.5	6.9	0.08	23.2	1.5	0.03
2b	74	30.5μM Zn^{2+} (+) Cd^{2+}, 30.5μM (day 28-74)	28.9	3.6	0.54	18.3	9.7	1.60	6.2	6.2	0.03
3a	78	122μM Zn^{2+}	22.3	2.4	0.03	17.8	7.8	0.05	22.0	1.6	0.03
3b	78	122μM Zn^{2+} (+) Cd^{2+}, 30.5μM (day 28-78)	36.2	4.1	0.36	23.1	7.1	1.80	26.0	2.1	0.05
4a	78	488μM Zn^{2+}	15.5	1.9	0.03	24.9	8.0	0.16	25.9	2.1	0.13
4b	78	488μM Zn^{2+} (—) Zn^{2+} (day 53-78)	27.2	3.7	0.04	23.1	11.0	0.08	21.4	2.3	0.06

* (+), added to previous supplement; (—), omitted from previous supplement.

Table 5.—*Temperature Changes of Rats Due to Zn^{2+} and Cd^{2+} Intake*

Group	Treatment*	Rectal Temperature (F) ± SE†	
		Day 21	Day 74
1a	No Zn^{2+}	97.7 ± 0.62(19)	...
1b	(+) Zn^{2+}, 30.5μM, day 28-74	...	...
2a	30.5μM Zn^{2+}	99.4 ± 0.30(10)	(8)96.2 ± 0.64
2b	30.5μM Zn^{2+} (Cd^{2+}, 30.5μM, day 28-74)	...	(4)95.4 ± 0.92
3a	122μM Zn^{2+}	99.3 ± 0.48(7)	(10)97.6 ± 0.53
3b	122μM Zn^{2+} ([+] Cd^{2+}, 30.5μM day 28-74)	...	(4)95.4 ± 0.29
4a	488μM Zn^{2+}	100.0 ± 0.91(4)	(4)98.5 ± 0.29
4b	488μM Zn^{2+} ([—] Zn, day 53-78)	...	(5)97.6 ± 0.81

* (+) or [+], added to previous supplement; [—], omitted from previous supplement.
† Numbers in parentheses indicate number of animals tested.

Summary and Conclusions

Male rats on a zinc-deficient diet responded directly and rapidly in growth to administration of zinc in the drinking water, and those receiving greater than optimal amounts of zinc ceased growing upon its removal from the diet. Blood and kidney zinc concentrations also respond directly to the concentration of zinc in the water.

The response to zinc was inversely related in the cases of WBC, hematocrit, hemoglobin, and liver zinc concentration. An interaction with copper was seen in the inverse relationship of liver copper to zinc intake.

The concomitant oral administration of low levels of cadmium (30.4μM in drinking water) had a pronounced effect on growth of rats if the zinc intake was low (zinc-cadmium ratio, 1:1), but it had no effect on growth when the zinc intake was higher (zinc-cadmium ratio, 4:1), indicating the antagonism between cadmium and zinc even at low doses of cadmium.

When the zinc-cadmium ratio was 1:1 blood zinc and copper were elevated, and when the ratio was 4:1 (where growth was not retarded) the zinc and copper levels were elevated in the kidney but not in blood.

Cadmium was elevated in blood, liver, and kidney whether the zinc-cadmium ratio was 1:1 or 4:1, but the cadmium level in liver appeared to be less when the ratio was higher. No marked concentration of cadmium was detected in the testes and no specific pathological findings due to cadmium could be found in the gonads.

The characteristic pathology of zinc deficiency was found in the group receiving no supplemental zinc. In other groups with suboptimal zinc, some of the characteristics of zinc deficiency were present. These were magnified by concurrent administration of cadmium.

It was found that the rectal temperature of the rats was directly influenced by the amount of zinc in the diet. Cadmium reduced core temperatures regardless of the zinc intake in these experiments.

David W. Yeager obtained the metal analyses and Donna Bowman carried out some of the nutritional aspects of this study.

These studies were carried out under Public Health Service grants ES-00159 and EC-00391.

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