79. The Absorption and Excretion of Zinc

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Zinc is now recognized to be one of the physiological elements, since it is essential for the growth of rats, and forms part of the carbonic anhydrase system [Shohl, 1939; Keilin & Mann, 1940]. Many foodstuffs contain comparable amounts of Fe and Zn, and the two metals tend to vary together. Thus white flour, egg-white and fish are poor sources of both, whereas brown flour, egg-yolk and meat are the reverse. There are, however, exceptions to this generalization. Milk contains three to five times as much Zn as Fe and the inside leaves of cabbage more Zn than the outer leaves [Sylvester & Hughes, 1936], whereas the reverse is true for Fe, and incidentally for Ca. Yeast, oysters and one or two exotic foods are very rich sources of Zn, but not necessarily of Fe.

The metabolism of Zn has not been fully worked out, although the subject has attracted attention from time to time, mainly owing to the extensive use of Zn in industry. Some excellent pioneering work was done by Röst & Weitzel [1918-19], Bachelor, Fehnel, Thomson & Drinker [1926], Drinker, Fehnel & Marsh [1927], and an informative review of the subject was published by Lutz [1926]. It had been established by that date that the normal human intake of Zn was of the order of 10-15 mg./day and that most of this was excreted in the faeces. Drinker *et al.* [1927] studied the Zn metabolism of two subjects for a week, in the middle of which a meal very rich in Zn was consumed. The urinary excretions did not rise, but within the next 24 hr. much additional Zn was passed in the faeces. Within the past 10 years the treatment of diabetics with Zn protamine insulin has been introduced and gained considerable popularity. The quantities of Zn administered are small, but they are given by subcutaneous injection and would amount to about 0.1 mg. of Zn per day in a patient who was receiving 50 units of Zn protamine insulin. The excretion of Zn after injection has been very little studied, although this seems the only way of finding out whether Zn is, or is not, freely excreted into the alimentary canal.

In 1938, metabolism experiments on six normal people were undertaken to study the fate of injected Ca, Mg, Fe and Zn. The way in which these experiments were done, and the results for Ca, Mg and Fe, have already been published [McCance & Widdowson, 1938; 1939]. In 1940-41 metabolism experiments were carried out to investigate the effects of brown and white bread on Ca absorption [McCance & Widdowson, 1942 *a*]. These presented opportunities of making further experiments with Zn, and work on patients has also been possible from time to time. Some 45 Zn 'balances', each lasting for about a fortnight, have been carried out on twelve persons, and Zn has been injected intravenously into ten of them. Particulars about the subjects and the technical aspects of the experiments may be found in the papers to which reference has already been made. Zinc determinations were made on the ash extracts of foods, urines and faeces, the method used being that described by Keilin & Mann [1940].

RESULTS

Zn balances at different levels of intake

Table 1 shows the Zn balances of three persons, one of them at two, and two of them at three, different levels of Zn intake. The low intakes were the result of specially planned diets. E.B.'s and E.W.'s moderate intakes were obtained when white flour constituted

Table 1. *Zn balances at different levels of intake*

Subject	Intake mg./day	Output, mg./day			Balance mg./day
		Urine	Faeces	Total	
E.W. ♀	5.6	0.4	5.2	5.6	± 0.0
	9.9	0.4	9.6	10.0	-0.1
	19.6	0.3	18.2	18.5	+1.1
E.B. ♂	4.9	0.4	5.3	5.7	-0.8
	13.8	0.1	11.0	11.1	+2.7
	22.0	0.4	19.0	19.4	+2.6
R.H.E. ♂	6.1	0.3	6.0	6.3	-0.2
	9.1	0.3	8.5	8.8	+0.3

40–50 % of their total calories, the rest of the diet being mixed. Their high intakes were achieved by substituting wheatmeal of 92 % extraction for the white flour. R.H.E.'s higher intake was due to the ingestion of Zn salts. These results typify so well the many others which have been obtained that it is unnecessary to give the whole set. They show the subjects in approximate balance at all levels of intake. They show that the urinary excretions were exceedingly small, smaller in fact than those recorded by Röst & Weitzel [1918–19], Bachelor *et al.* [1926], Drinker *et al.* [1927] and Fairhall & Hoyt [1929]. The concentration of Zn in normal urine would seem to be of the same order as that in London tap water [Alport & Moon, 1939]. Scoular [1939] recorded still lower values, but since they were found in children the figures are not really comparable. Table 1 also shows that increasing the intake made no difference to the urinary excretion. This is a point of cardinal importance. It suggests that in normal life the kidney can take little or no part in regulating the amount of this metal in the body. Zn, therefore, resembles Fe in this respect and differs from Na, K, Ca and Mg, all of which are excreted by the kidney in amounts which vary with the requirements of the body and the amounts absorbed [McCance & Widdowson, 1942*b*].

The fate of injected Zn

In these experiments the intake by mouth and the output in the urine and stools have been measured for 4 or 5 weeks, and during the 3rd and 4th weeks 58–86 mg. Zn have been injected intravenously in twelve to fourteen divided doses. Most of the subjects have had only a single course of injections, but two had a second course after an interval. In the first experiment it was decided to use Zn protamine, and Messrs Boots very kindly prepared and presented a solution containing 2 mg. of Zn per ml. Unfortunately, the protein in this preparation produced unpleasant reactions on the second day, so inorganic Zn salts were substituted. These were dissolved in a convenient volume of 0.9 % NaCl and sterilized in the autoclave. The injections have been given at whatever hour of the day was most convenient and the time taken over them has never been less than 5 and has sometimes been as long as 40 min. In the earlier experiments Ca, Mg and Fe were given at the same time; in the later experiments the Zn was administered alone. These variations in the times and methods of administration have not appeared to influence the results in any way.

The results of nine experiments are given in Table 2. In one sense the subjects gave absolutely concordant results. The increases in urinary excretion were insignificant even when quite large amounts were injected. In R.M., M.M. and R.M.L. there was no increase, but Ca or Mg salts, injected at the same time, were quantitatively excreted [McCance & Widdowson, 1939]. Evidently, the kidney does not vary its excretion of Zn in accordance with the amount in the plasma or the amount absorbed. The traces constantly found in the urine may represent the end product of some quite different, possibly metabolic, function of the kidney. If so, the urinary excretion of Zn would be analogous to the intestinal excretion of Ca and Mg. Owing to the presence of

Table 2. *The fate of Zn given intravenously*

Subject	Intake, mg./day		Output, mg./day			Balance (excluding injected Zn) mg./day
	Mouth	Injection	Urine	Faeces	Total	
B.A. ♀	11.6	0.0	0.3	10.0	10.3	+1.3
	10.9	5.0	0.8	12.4	13.2	-2.3
E.B. ♂	5.7	0.0	0.5	6.7	7.2	-1.5
	5.7	6.0	0.9	9.0	9.9	-4.2
R.M. ♂	6.7	0.0	0.6	5.9	6.5	+0.2
	6.3	4.0	0.6	8.7	9.3	-3.0
K.B. ♀	10.7	0.0	0.5	10.3	10.8	-0.1
	12.4	6.0	0.8	11.6	12.4	±0.0
R.M.L. ♂	5.8	0.0	0.4	5.5	5.9	-0.1
	6.7	4.0	0.4	6.3	6.7	±0.0
R.H.E. ♂	6.1	0.0	0.3	6.0	6.3	-0.2
	7.1	4.0	0.4	7.8	8.2	-1.1
M.M. ♀	6.1	0.0	0.3	5.1	5.4	+0.7
	6.2	4.0	0.3	8.3	8.6	-2.4
E.W. ♀	7.8	0.0	0.4	7.6	8.0	±0.2
	8.8	4.0	0.5	10.2	10.7	-1.9
Patient Ar. ♀	10.3	0.0	<0.1	9.2	9.3	+1.0
	11.8	6.2	0.3	17.1	17.4	-5.6

these two metals in the digestive juices, some excretion of both into the gut is inseparable from the alimentary functions of this organ. The amounts so excreted, however, are not ordinarily related to anything else, and certainly not to small changes in plasma concentration.

During the control periods four of the subjects were in slightly positive, and five in slightly negative, Zn balance. The averaged results for the group show an almost exact balance. Seven of the subjects responded to the injection of Zn by excreting more of the metal than they were obtaining in their food. Two did not, and the additional amounts put out by the others varied from one subject to another and were never as great as the quantities which had been injected. For this reason the results have not been averaged, and it was on account of this lack of uniformity in the response of the subjects that the experiments carried out in 1938 were not published at that time. The subjects, however, have not responded more uniformly in the later experiments, and it is now felt that these irregularities are physiological, not technical, in origin. It would seem, therefore, that the human body possesses a means of getting rid of an excess of Zn from its tissues, but that the sensitivity of the regulating mechanism to a given dose varies with the individual and possibly with the degree of saturation of his storage organs. It is interesting to find the intestinal route the one selected by Nature for the excretion of a physiological metal. Owing to its absorptive functions the intestine can never achieve such a fine adjustment as the kidney, and can only act effectively for a non-toxic ion likely to present itself in very small amounts and forming relatively insoluble salts. Mn is such a metal, and it seems to be excreted very much like Zn [Kent & McCance, 1941]. Fe has the requisite properties, but does not appear to be excreted at all. It is interesting to picture the state of affairs which would result if the large intestine was the only part of the body which could deal with the excretion of Na salts.

From the small number of papers which have been published on the subject, it is probable that the response of animals to Zn injections will be found to be similar to that of human beings. Salant, Rieger & Treuthardt [1918] injected Zn into rabbits and cats in quantities relatively greater than those used in the present experiments, and subsequently found very little in the urines, but quantities up to half the amounts injected in the intestinal tracts. It is not clear from their paper, however, whether due allowance was made for the Zn in the animals' food, and particularly in that of the rabbits.

The excretion of Zn in patients with albuminuria

Since Zn salts will readily precipitate plasma proteins, it must be supposed that most of the Zn in the plasma is so combined. This would explain why the urine contains so little Zn, and why injecting Zn does not provoke any excretion of the metal in the urine. The same explanation probably underlies the fact that normal urines are practically Fe-free. If this is the case, patients with albuminuria might be expected to excrete more Zn in their urines than normal persons. Fairhall & Hoyt [1929] made a survey of this subject and came to the conclusion that the amount of Zn in the urine bore no relationship to the degree of albuminuria, but they did find high concentrations of Zn in the urine of nephritics. They noted, however, that the daily excretions of such patients were not greater than those of normal subjects and they commented on the possibility that the daily outputs of metal might have been abnormally high, had the volumes of urine passed by the nephritics not been so low. It was decided to re-examine the matter, and measurements were made of the daily excretion of Zn by a number of patients with moderate and heavy albuminuria. The greatest care was taken to ensure that the patient, bed, bedding and collecting vessels were free of all ZnO or dusting powder. The figures were far outside the range of those of the present series obtained from normal persons. The actual figures for six patients ranged from 1.0 to 3.8 and averaged 2.1 mg./day, whereas the normal ones varied from 0.11 to 0.50 and averaged 0.29 mg./day. Thus the urinary excretions were about seven times the normal size in patients with albuminuria. It was confirmed, however, that the amount of Zn excreted was not directly correlated with the degree of albuminuria. Determinations of the plasma Zn might have helped to establish some correlation, but unfortunately none were made. The urinary excretion of vitamin A may be recalled in this connexion [Lawrie, Moore & Rajagopal, 1941]. The vitamin is excreted only by patients with protein or proteose in the urine, but there is no quantitative correlation between the two excretions.

In normal persons the urinary excretion of Zn (as of Fe) may almost be neglected in balancing up intakes and outputs, but this is not the case in some patients with albuminuria. A study of such persons offered a method of finding out something about the ease with which Zn was absorbed and also about the intestinal exchanges. One would expect that, if Zn were freely absorbed and the surplus excreted back into the gut, patients who were losing much Zn in their urines would excrete less Zn in their faeces than they took in their food, and not as normal subjects almost the same amount. Balance experiments, therefore, were carried out on two patients and the results are shown in Table 3. It will be seen that neither subject appeared to be absorbing any Zn,

Table 3. *Zn balances of patients with heavy albuminuria*

Subject	Intake mg./day	Output, mg./day			Balance mg./day
		Urine	Faeces	Total	
M.E.	13.9	3.0	15.3	18.3	-4.4
H.E.	13.7	2.3	13.8	16.1	-2.4

yet M.E. was losing 3 mg. and H.E. 2.3 mg./day in the urine. One must conclude from these limited experiments that Zn is not freely absorbed and that patients with albuminuria may not absorb the metal rapidly enough from ordinary diets to make good their urinary loss. Indeed, if they were to live long enough, they might even become short of Zn. Symptoms of Zn deficiency in human beings have, however, never been described. If it is true that adults absorb very little Zn, then very little must normally be excreted into the gut. This function, therefore, is only exerted strongly in the abnormal circumstances occasioned (in these experiments) by an injection of Zn.

SUMMARY

1. 45 Zn balances have been carried out on normal persons and on patients.
2. Normal persons excreted about 0.3 mg./day in the urine. This amount did not vary with the intake by mouth, nor was it appreciably raised by intravenous injections.
3. Patients with albuminuria excreted about seven times the normal amount of Zn in their urine.
4. Within the limits of experimental error, normal adults excreted almost the same amount of Zn in their stools as they ingested in their food. Some adults excreted additional Zn in their faeces when amounts up to 6 mg./day were injected intravenously for a fortnight; others did not.

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