LXIV. THE FATE OF CALCIUM AND MAGNESIUM AFTER INTRAVENOUS ADMINISTRATION TO NORMAL PERSONS

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FIFTEEN years ago there would seem to have been no doubt in the minds of physiologists that the divalent and trivalent metals were excreted mainly by the gastro-intestinal tract and that variations in the rate of this excretion maintained the normal levels within the body. This is still the opinion of most people who have not studied the subject, but within the last 10 or 12 years evidence has been collected which makes it essential to reconsider the whole question.

First, it has been shown that iron is certainly excreted much less freely than was previously supposed [McCance & Widdowson, 1937, 1]. It is, in fact, impossible to demonstrate any gastro-intestinal excretion of iron by man [Widdowson & McCance, 1937; McCance & Widdowson, 1938], although it is agreed that traces of this metal must get into the intestine from abraded cells and glandular secretions. It has, therefore, been suggested that the amount of iron in the body must be regulated by controlled absorption [McCance & Widdowson, 1937, 2] and this seems to have been supported by the most recent evidence [Hahn *et al.* 1938]. Secondly, much recent work on Ca has tended to show that in normal circumstances its excretion into the gastro-intestinal tract is negligible or at least plays no part in regulating the amount in the body [Christiansen, 1936; Aub *et al.* 1937; Henry & Kon, 1939]. The best evidence has been obtained (a) by the direct determination of the Ca excreted into the isolated large intestines of dogs [Nicolaysen, 1934] and men [Welch *et al.* 1936; Johnson, 1937], (b) by the determination of Ca balances under experimental conditions usually involving the parenteral administration of the metal [Nicolaysen, 1934; Christiansen, 1936; Albright & Sulkowitch, 1938]. Against this view, however, must be set certain rather older experiments such as those of Greenwald & Gross [1925] on dogs, Ross & Scriver [1928] and Pugsley [1932] on rats. From a study of faecal pellets Cowell [1937] also considers that rabbits excrete Ca into their large intestines. This excretion may be peculiar to the rabbit and in any case it probably has no regulatory function [Christiansen, 1936]. If the balance experiments which have been carried out on normal persons and on hyperthyroid patients are correct, relatively large quantities of Ca may be passed into the human gastro-intestinal tract, even when the food contains very little [Bauer *et al.* 1929; Tibbetts *et al.* 1932; Tibbetts & Aub, 1937, 2]. There is nothing to suggest however that this excretion has any regulatory function, but nevertheless, it requires further investigation. Thirdly, what little work has been carried out on Mg has also tended to show that this metal is not excreted in more than very small quantities into the gastro-intestinal tract [Ferguson & Ivy 1936; Nicolaysen, 1936].

In contrast to this it still appears true to say that certain non-physiological heavy metals are excreted predominantly by the gastro-intestinal tract. Thus,

lead and radium have been shown to be so excreted when they have been given parenterally or when they have been mobilized from the bones by parathormone [Hunter & Aub, 1926-7; Schlundt & Failla, 1931; Aub, 1935; Aub *et al.* 1938]. Mercury has been found to be excreted—slightly at any rate—in the faeces after parenteral administration [Young *et al.* 1930]. The site of the excretion of these metals, however, is not yet known. Histological attempts have been made to solve the problem [Schönlebe, 1937], but physiological experiments should be undertaken, similar to those which have already been carried out for Ca and Fe on animals with isolated large intestines.

The experiments now to be described were undertaken in conjunction with work on the excretion of Fe [Widdowson & McCance, 1937; McCance & Widdowson, 1938]. They are, it is believed, the first of their kind to be made on strictly normal persons, and the results are in keeping with the view that the amount of Ca or of Mg in the body is not regulated by glands which secrete into the gastrointestinal tract.

EXPERIMENTAL ARRANGEMENT AND TECHNIQUE

The work was carried out at King's College Hospital, London, on the same six persons already described [McCance & Widdowson, 1938]. Balance experiments were performed at two different (physiological) levels of intake by mouth and finally during a time of parenteral administration. Each balance experiment lasted 14 days and was preceded by a preliminary period of 2 or 3 days. The dietary regime was continued beyond the 14 days until the last specimen of faeces had been collected. Distilled water was used for drinking purposes and in the preparation of beverages. The use of toothpaste was avoided. The increased oral intake of Ca was brought about by increasing the intake of milk and that of Mg by administering medicinal supplements. Both metals were injected intravenously as the gluconates; the method of so doing was described by McCance & Widdowson [1938]. 0.186 g. of Ca and 0.219 g. of Mg were given daily. Even run in slowly over a period of 30-45 min. the intravenous injection of these amounts to normal persons is rather an uncomfortable experience, for it is accompanied by constant flushings and sometimes by nausea, but no further difficulties were encountered except that one subject (R. M. L.) fainted at the close of his 7th injection. The management of the food, drinks, urine and faeces has been described by McCance & Widdowson [1938] and the chemical methods employed were those described by McCance *et al.* [1936].

RESULTS

(1) *Calcium*

Table I shows the results for the six subjects at the lower levels of intake which varied from 6.43 to 9.20 g. Ca in the 14 days—an average of 0.582 g. Ca/subject/day. R. A. M. and R. H. E.'s balances were rather unaccountably negative but the summarized results amounted to a negative balance of only 2.03 g. on an intake of 49 g.

Table II gives the results at the higher levels of intake by mouth which now varied from 8.10 to 12.88 g. Ca in the 14 days and averaged 0.734 g. Ca/subject/day. R. A. M. and R. H. E. were still in negative balance and it should be pointed out that these negative balances cannot be explained by incomplete collections of faeces for at this stage both subjects were in positive iron balance [McCance & Widdowson, 1938]. The summarized results showed the group to be practically in balance.

Table I. *Ca balances at the lower levels of intake*

Subject	Ca intake from food, g.	Ca output, g.			Ca balance, g.
		Urine	Faeces	Total	
E. M. W.	9.20	1.34	7.50	8.84	+0.36
M. M.	8.61	2.20	6.86	9.06	-0.45
H. L.	6.43	0.64	5.72	6.36	+0.07
R. A. M.	7.82	2.49	6.37	8.86	-1.04
R. M. L.	8.84	2.81	5.75	8.56	+0.28
R. H. E.	7.98	2.50	6.73	9.23	-1.25
Totals	48.88	11.98	38.93	50.91	-2.03

Table II. *Ca balances at the higher levels of intake*

Subject	Ca intake from food, g.	Ca output, g.			Ca balance, g.
		Urine	Faeces	Total	
E. M. W.	11.35	1.70	9.81	11.51	-0.16
M. M.	11.92	2.47	9.40	11.87	+0.05
H. L.	8.10	0.87	7.10	7.97	+0.13
R. A. M.	8.97	2.42	7.10	9.52	-0.55
R. M. L.	12.88	3.53	9.12	12.65	+0.23
R. H. E.	8.46	2.70	6.46	9.16	-0.70
Totals	61.68	13.69	48.99	62.68	-1.00

Table III contains the results when Ca was administered intravenously. The oral intakes varied from 7.09 to 9.78 g. Ca in the 14 days—an average of 0.628 g. Ca/subject/day. Neglecting for the moment individual results, it is evident that additional Ca, equivalent to a very great part if not the whole of the Ca administered intravenously, had been excreted before the experiment came to an end, since the summarized results for the group indicated a positive balance of only 2.52 g. on an intake of 68.31 g. Unfortunately it is not possible to define the limits of error in an experiment of this kind, but from the individual results it would appear that R. M. L. and possibly R. H. E. had not excreted as much additional Ca as had been injected into them by the end of the experiment—but that the others had certainly done so.

Table III. *Ca balances during intravenous administration of the metal*

Subject	Ca intake, g.			Ca output, g.			Ca balance g.
	From food	From injection	Total	Urine	Faeces	Total	
E. M. W.	8.54	2.60	11.14	3.37	7.37	10.74	+0.40
M. M.	9.00	2.60	11.60	5.04	6.59	11.63	-0.03
H. L.	7.09	2.60	9.69	2.74	6.27	9.01	+0.68
R. A. M.	9.78	2.60	12.38	5.21	8.11	13.32	-0.94
R. M. L.	9.40	2.60	12.00	4.75	5.92	10.67	+1.33
R. H. E.	8.90	2.60	11.50	4.17	6.25	10.42	+1.08
Totals	52.71	15.60	68.31	25.28	40.51	65.79	+2.52

Table IV shows the ratios of urinary/faecal Ca and faecal/food Ca of all the subjects during each stage of the experiment. The relative constancy of the urinary/faecal ratio at both levels of intake by mouth suggests that during the period of high Ca intake the metal was divided between the urine and faeces in about the same proportions as it had been at the lower level of intake. The large increase in the ratio during intravenous administration indicates that in these circumstances most of the additional Ca was being excreted in the urine. In

Table IV

Subject	Ratios Urinary Ca/Faecal Ca			Ratios Faecal Ca/Food Ca		
	Lower intakes	Higher intakes	Injection stage	Lower intakes	Higher intakes	Injection stage
E. M. W.	0.18	0.17	0.46	0.82	0.87	0.86
M. M.	0.32	0.26	0.77	0.80	0.79	0.73
H. L.	0.11	0.12	0.44	0.89	0.88	0.88
R. A. M.	0.39	0.34	0.64	0.81	0.79	0.83
R. M. L.	0.49	0.39	0.80	0.65	0.71	0.63
R. H. E.	0.37	0.42	0.67	0.84	0.76	0.70
Average	0.31	0.28	0.63	0.80	0.80	0.77

fact, since there was no rise in the faecal/food Ca ratios during this time, it is clear that all the additional Ca, equivalent to the whole or almost the whole of the amount injected, must have been excreted by the kidney.

It is possibly of some interest to note that although the urinary/faecal Ca ratio is remarkably constant in any one individual it varies considerably from one individual to another. The findings of Owen [1939] in a study of 10 adult and elderly males were very much the same. Thus about 30 % of R. M. L.'s total output of Ca was found in the urine, whereas only about 10 % of H. L.'s. It would be an interesting problem to find out why this should be so. In the light of the experiments in which Ca was given intravenously, it would look as though H. L. consistently absorbed less Ca than did R. M. L. It may further be noted that the three female subjects (E. M. W., H. L., and M. M.) had the three lowest urinary/faecal Ca ratios, but it is impossible to say whether this represents a real sex difference since the number of subjects was so small. The work of Owen [1939] suggests that occasionally males may excrete as little as 10–11 % of their total Ca in the urine.

(2) *Magnesium*

Table V shows the results for the six subjects at the lower levels of intake, which varied from 3.21 to 4.44 g. Mg in the 14 days, an average of 0.271 g. Mg/person/day. On those amounts of Mg all the subjects were in fair balance and the summarized results amounted to an insignificant positive balance of 0.22 g. on an intake of 22.8 g.

Table V. *Mg balances at the lower levels of intake*

Subject	Mg intake from food, g.	Mg output, g.			Mg balance, g.
		Urine	Faeces	Total	
E. M. W.	3.40	1.51	2.25	3.76	-0.36
M. M.	3.87	1.44	2.36	3.80	+0.07
H. L.	3.21	1.07	2.10	3.17	+0.04
R. A. M.	4.44	1.74	2.52	4.26	+0.18
R. M. L.	3.98	1.81	1.95	3.76	+0.22
R. H. E.	3.90	1.71	2.12	3.83	+0.07
Totals	22.80	9.28	13.30	22.58	+0.22

Table VI indicates the results on the higher levels of intake by mouth, which varied from 5.18 to 6.38 g. Mg in the 14 days and averaged 0.405 g. Mg/subject/day. All the subjects were again in very fair balance and the summarized results again amounted to a small positive balance of 0.73 g. on a total intake of 34 g.

Table VI. *Mg balances at higher levels of intake*

Subject	Mg intake, g.			Mg output, g.			Mg balance g.
	From food	From medicine	Total	Urine	Faeces	Total	
E. M. W.	3.51	1.76	5.27	1.71	3.41	5.12	+0.15
M. M.	3.57	1.76	5.33	1.18	3.88	5.06	+0.27
H. L.	2.78	2.40	5.18	1.38	3.84	5.22	-0.04
R. A. M.	3.98	2.40	6.38	1.85	4.23	6.08	+0.30
R. H. L.	3.79	1.76	5.55	2.18	3.45	5.63	-0.08
R. H. E.	3.90	2.40	6.30	2.18	3.99	6.17	+0.13
Totals	21.53	12.48	34.01	10.48	22.80	33.28	+0.73

Table VII gives the results when Mg was administered intravenously. The oral intakes ranged from 3.20 to 4.28 g. in the 14 days, and averaged 0.279 g. Mg/subject/day. 3.06 g. Mg were given intravenously to each subject (0.219 g./day). It is evident from the balances that, as with Ca, additional Mg equal to practically the whole of the quantity given intravenously had been excreted before the experiment terminated. The summarized results showed a positive balance of 2.19 g. on a total intake of 41.78 g. The individual results suggest that M. M. was the only subject who had not got rid of the injected Mg.

Table VII. *Mg balances during the intravenous administration of the metal*

Subject	Mg intake, g.			Mg output, g.			Mg balance g.
	From food	From injection	Total	Urine	Faeces	Total	
E. M. W.	3.75	3.06	6.81	4.53	2.10	6.63	+0.18
M. M.	3.79	3.06	6.85	3.39	2.15	5.54	+1.31
H. L.	3.20	3.06	6.26	3.77	2.21	5.98	+0.28
R. A. M.	4.14	3.06	7.20	3.98	2.47	6.45	+0.75
R. M. L.	4.26	3.06	7.32	4.75	3.16	7.91	-0.59
R. H. E.	4.28	3.06	7.34	4.77	2.31	7.08	+0.26
Totals	23.42	18.36	41.78	25.19	14.40	39.59	+2.19

Table VIII

Subject	Ratios Urinary Mg/Faecal Mg			Ratios Faecal Mg/Ingested Mg		
	Lower intakes	Higher intakes	Injection stage	Lower intakes	Higher intakes	Injection stage
E. M. W.	0.67	0.50	2.16	0.66	0.65	0.56
M. M.	0.61	0.30	1.58	0.61	0.73	0.57
H. L.	0.51	0.36	1.70	0.65	0.74	0.69
R. A. M.	0.69	0.44	1.62	0.57	0.66	0.60
R. M. L.	0.93	0.63	1.50	0.49	0.62	0.74
R. H. E.	0.81	0.55	2.07	0.54	0.63	0.54
Average	0.70	0.46	1.77	0.58	0.67	0.62

Table VIII gives the ratios of urinary/faecal Mg and faecal/food Mg of all the subjects during each stage of the experiment. The fall in the urinary/faecal ratio during the higher oral intakes indicates that excretion of the additional Mg was not shared in the previous proportions between the urine and faeces. Tibbetts & Aub [1937, 1] also found this to happen but their Mg supplements were much larger. Indeed, a comparison of the summarized results of Tables V and VI suggests that the kidney excreted very little of the extra Mg taken by mouth, and in this respect the results differ from those obtained with Ca. In all probability very little of the extra Mg taken by mouth was absorbed. The large increase

in the urinary/faecal ratio during the fortnight of intravenous administration indicates that, as in the case of Ca, the kidney was excreting much of the extra Mg, and a study of the food/faecal ratios shows that, as with Ca, none of the additional Mg was finding its way into the faeces.

DISCUSSION

These experiments are only a small contribution towards the solution of a very large and complicated problem, but they raise interesting points which deserve consideration. They would seem to show, first, that the injection of Ca or Mg intravenously into normal persons provokes no increased excretion of these metals by the gastro-intestinal tract, and taken in conjunction with previous work they support the view put forward earlier in this paper that the gastro-intestinal tract does not excrete these metals in amounts which vary with the levels in the plasma or with the needs of the body. It would be very interesting to be able to say why lead and radium are treated so differently. Secondly, these experiments show quite clearly that Ca and Mg given intravenously to normal persons are rapidly excreted by the kidney, and it follows that the normal kidney must be exceedingly sensitive to variations in the levels of these metals in the serum. This mechanism must always be in operation and should be seriously considered whenever variations in the urinary excretion of these metals have to be explained. It would seem from the literature, however, that in hyperthyroidism and sometimes in hyperparathyroidism there may be a large increase in the output of Ca in the urine without a corresponding increase in the serum Ca, so that other factors are probably involved, at any rate in the case of this metal. In the absence of an acidosis in these diseases, which might be expected to raise the urinary excretion of these metals by increasing the concentration of ultra-filterable ions in the serum, this must be due to a change in the activity of the kidney itself. It would be most interesting and valuable to know in what way secretions of the thyroid and parathyroid affected the kidney.

SUMMARY

1. 0.186 g. Ca and 0.219 g. Mg were injected intravenously into six normal persons every day for a fortnight.
2. This led to a rapid increase in the excretion of Ca and Mg by the kidney and in most subjects the additional output was equal to the amount injected.
3. No evidence was found that any additional Ca or Mg was excreted into the gastro-intestinal tract.

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