CCXXVI. THE FATE OF STRONTIUM AFTER INTRAVENOUS ADMINISTRATION TO NORMAL PERSONS

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THE intestine generally, and the large intestine in particular, has long been thought to excrete Ca, Mg and Fe, and by so doing to play a large part in regulating the amounts of these metals within the body. In the last few years, however, several investigators have tested this theory experimentally, and shaken it to its foundations. It now appears probable that the intestinal excretion of these metals is small and may even be negligible. The intestine certainly has not the regulatory function once assigned to it. The subject has been briefly reviewed by McCance & Widdowson [1939], who have themselves injected Fe, Ca and Mg into normal persons, and failed to obtain any evidence of increased excretion by the intestine.

High concentrations of Sr are not unknown in biological tissues [Fox & Ramage, 1931; McCance & Masters, 1937], but in mammals only traces have been found [Gerlach & Müller, 1935]. Chemically, however, and to some extent physiologically [Haldane, 1925; Gerlach & Müller, 1935], Sr resembles Ca and it was felt therefore that an investigation of its excretion by man might not only be of interest in itself but might also throw light on the way in which Ca is excreted.

The literature shows that Sr has been used medicinally for a very long time. According to Loeser & Konwiser [1929-30] it was introduced into therapeutics by Vulpian in 1885, and in comparatively recent times it has been given both by mouth and vein in the treatment of a variety of diseases [Hesse, 1926; Hummel, 1928; Gassmann, 1938, etc.]. The elimination of Sr seems scarcely to have been studied, although Loeser & Konwiser [1929-30] state without reference that Sr "is eliminated by the intestines. The urine contains only traces of strontium when given subcutaneously". Haldane [1925] showed that after taking 60 g. of $\text{SrCl}_2 \cdot 6\text{H}_2\text{O}$ by mouth—which caused violent diarrhoea—1.46 g. of Sr (7.4 % of the amount taken) were excreted in the urine over the next 24 hr. No further urines were collected.

Experimental arrangement and technique

R. A. M., aged 40, male, and E. M. W., aged 32, female, were themselves the two subjects, and the experiments were timed to avoid E. M. W.'s menstrual periods. To obtain the basal excretion of Sr, if any, we arranged that for 11 preliminary days we should eat only simple foods which could be duplicated during later periods. After 3 days of this regime urine and faeces were collected for a period of 7 days. It was originally intended that during the experimental period the dietary programme should be repeated, that Sr should be injected intravenously each day for 1 week, and that the urine and faeces covering this period should be collected and examined for Sr. No after period was planned because,

when Ca had been given intravenously, the extra Ca excreted during the experimental period was equal to the amount injected. This scheme was carried out until five injections had been given; but then, owing to an accident, which came about in the following way, the subsequent arrangements had to be modified. At the commencement of the experimental period a solution of strontium lactate was made up containing 23.5 mg. Sr/ml. and enough sterilized, as was thought, to last till the end of the experiment. The solution, which appeared opalescent after being autoclaved, was injected slowly into an antecubital vein. 23.5 mg. were given to E. M. W. on the first day of her experiment but from the second day onwards it was decided to double the dose. R. A. M. commenced his experiment 1 day after E. M. W. and received 47 mg. on each day. Hence by the 5th day it was necessary to sterilize more of the original solution, which by this time had itself become slightly opalescent. This further sterilization was carried out without appreciating that the original solution had become heavily infected with bacteria. We gave the newly sterilized solution intravenously to each other about 11 to 11.30 a.m. on the 5th day of R. A. M.'s experimental period and on the 6th day of E. M. W.'s. In just under an hour we began to feel very ill. E. M. W. had a most intense headache, followed by pains in the back and thighs, rigors, vomiting and diarrhoea. R. A. M. had a much milder headache, rigors and severe pains in the back and thighs. Three to four hours after the injection we both had high temperatures which fell slowly throughout the evening and night. Some modification of the diet was unavoidable during this 24 hr., and on the morning following the accident we decided to omit the daily Sr as both of us were still feeling somewhat shaken, and to utilize the remaining days of the time available for this experiment as an after period. As it turned out this rather improved the experiment. Fortunately, the accident did not prevent the complete collection of the excreta.

During the preliminary period of 7 days the urines for the whole week were mixed for analysis. Toluene was used as a preservative. The faeces were collected in one vessel as described by Widdowson & McCance [1937]. In the experimental period the bladder was emptied each day just before the Sr was given intravenously, and again 2 hr. later. These 2 hr. specimens were mixed under toluene and analysed separately from the urine passed throughout the rest of the 24 hr. The faeces were collected as during the preliminary period. Those passed on the day of the accident by E. M. W., and those passed on the following day by R. A. M. were analysed separately but the results have been included with those of the experimental period in Table I A and B. Duplicate portions of 250 ml. of urine were strongly acidified with H_2SO_4 , evaporated in silica crucibles and ashed at about 450° . The faeces were treated with HNO_3 and ashed [Widdowson & McCance, 1937]. All the ashes were weighed and transferred to small, well-stoppered vaccine bottles.

With the co-operation of Mr N. L. Kent the excretion of Sr was followed spectrographically. Such a method has not the accuracy of a good chemical determination, but it has advantages which were considered to outweigh this. Firstly, spectrographic methods are highly specific, and secondly they are exceedingly "micro". Both these attributes are most important in following "trace" elements, and in this study they enabled much smaller quantities of Sr to be injected during the experimental period than would otherwise have been necessary. Thus the general metabolism of Ca was less likely to be upset. The determinations could not be made by Ramage's filter paper method [Sheldon & Ramage, 1931] because the Sr lines did not appear satisfactorily on the plate even when Sr was known to be present in the sample, or had been

added. In passing it may be mentioned that since Sheldon & Ramage employed this method, they may have failed to detect Sr in many of the mammalian tissues examined by them. The determinations were therefore made by the arc method. Brass electrodes were used and a great many exposures were made to get the "unknowns" and the "standards" close to each other both in strength and position. The standard solutions were made by adding known amounts of Sr to the urine of R. A. M.'s preliminary period.

Results

Table I A shows the results of R. A. M.'s experiment. It will be seen that during the preliminary period a little more Sr was found in the urine than in the faeces, and that the weekly excretion amounted to 24 mg. The urinary output for the 2-hourly experimental periods which followed the injection of Sr was 15–20 times higher than it had been during the preliminary period, and an output 10 times as great was maintained throughout the rest of the experimental period. The faecal excretion was barely doubled. A high rate of urinary excretion was maintained throughout the after period, and by the end of the experiment 57 % of the injected Sr had been excreted. 93 % of the "recovered" Sr was eliminated by the kidney.

Table I. *Strontium excretion, R. A. M. (A) and E. M. W. (B)*

	A mg.	B mg.
Preliminary period (7 days):		
Urinary excretion of Sr/hr.	0.084	0.183
Faecal excretion of Sr/hr.	0.058	0.042
Sr excreted in the preliminary period	24	38
Experimental period (R. A. M. 5 days; E. M. W. 6 days):		
Urinary excretion of Sr/hr. for the 2 hr. following Sr injections ...	1.40	0.73
Urinary excretion of Sr/hr. throughout the rest of the 24 hr. ...	0.82	0.69
Faecal excretion of Sr/hr.	0.11	0.099
Sr excreted in the experimental period	118	114
After period (2 days):		
Urinary excretion of Sr/hr.	0.72	0.29
Faecal excretion of Sr/hr.	0.12	0.0
Sr excreted in the after period	40	14
Sr injected	235	258
Sr recovered (Sr excreted in the experimental and after periods minus the amount excreted in the preliminary period) ...	134	85
Sr recovered (as % of the amount injected)	57 %	33 %

Table I B shows E. M. W.'s results and in essentials they resemble those of R. A. M. One or two minor differences should be mentioned. Firstly, the urinary excretion of Sr during the preliminary period is surprisingly high when one considers R. A. M.'s urinary/faecal ratio at this time and the well-known urinary/faecal excretion ratios for Ca. The urine may have been contaminated but there is no reason for this assumption. During the experimental period the urinary output of Sr did not rise so high as did that of R. A. M. and the faecal output did not appear to rise at all till the day of the accident when a relatively large output of Sr accompanied the diarrhoea. The average for the 6 days indicates a small increase. Only 33 % of the injected Sr had been recovered by the end of the experiment, and even supposing the preliminary urine to have been contaminated the amount recovered would probably not have exceeded 40 %; 88.5 % of the "recovered" Sr was found in the urine.

DISCUSSION

These results show that the kidney is the organ primarily responsible for the excretion of Sr once it has been absorbed from the gut. They lend no support whatever to the statement in Loeser & Konwiser's [1929-30] article. There are, however, dozens of similar statements about Ca and Fe in the literature, and they are all expressions of the fact that the old theory had been dominant for so long that it had become accepted without question. It is probable from the slow rate at which Sr is excreted that it escapes to the tissues very soon after injection, where possibly it may displace an equivalent amount of Ca, and whence it may only slowly find its way back into the general circulation to become available for excretion. This slow rate of elimination is important, for injected Ca is excreted much more rapidly [McCance & Widdowson, 1939]—possibly because the tissues are already saturated with this element. It was thought that Ca might be eliminated so rapidly by the kidney that the intestinal excretion never had a chance to come into action, and that therefore injecting Ca was not a fair test of the intestinal path of excretion. The same criticism cannot be made of this study. The fact that there is a small increase of Sr excretion in the faeces is an interesting feature of these experiments, although E. M. W. did not show any increase till the day on which the accident happened. Assuming the increase to be a true one, however, it suggests that injected Sr finds its way into the intestinal juices and possibly replaces an equivalent amount of Ca therein. The results in general terms support the view that the intestinal excretion of Ca or Mg is unlikely to play an important part in regulating the amounts of these metals within the body.

SUMMARY

1. 47 mg. of strontium were injected intravenously every day for 5 days into two normal adults. A smaller preliminary dose was given to one.
2. The strontium was excreted slowly and about 90 % of it by the kidney.

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