Effect of Combined Use of Calcium Gluconate and Ammonium Chloride on Removal of Sr^{85} in Man Two Weeks after Exposure.* (26922)

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Studies of the metabolism of radioactive strontium in man(1,2) and of the enhancement of its excretion have been previously reported from this laboratory(3-5). An increase of the urinary calcium excretion induced by intravenously administered calcium and/or orally administered ammonium chloride was shown to be accompanied by a considerable increase of urinary radiostrontium excretion(1,3,5). The possibility of inducing an increase of radiostrontium excretion by orally administered ammonium chloride as late as 2 weeks after injection of the Sr^{85} tracer has been demonstrated(3). This relatively late removal is of interest since radiostrontium is assumed to be mainly deposited in tissues, including bone, at that time. Since the combination of intravenously injected calcium and orally administered ammonium chloride was more effective than either agent alone at the time of injection of the Sr^{85} tracer, in the so-called "early" phase of the study, the effectiveness of this combined regimen 2 weeks after exposure was investigated. These data are reported here.

Materials and methods. Six patients were studied on a constant, analyzed, dietary intake under strictly controlled conditions on the Metabolic Research Ward. Duration of the studies ranged from 19 to 28 days. The age, sex and diagnoses of the patients and the studies performed are listed in Table I.

A single tracer dose of Sr^{85} (0.1-0.2 μc/kg body weight) was given intravenously on the first day of the control and experimental studies. Plasma levels of Sr^{85} were determined at 1, 4, 8 and 24 hours following injection of the tracer, daily for 6 days thereafter and 3 times per week for as long as significant counts could be obtained with the equipment available. The urinary output of the first day of the study was collected in fractions, for radioassays and calcium analyses, at time intervals at which blood samples were obtained. Thereafter, urinary Sr^{85} and calcium excretions were determined daily on aliquots of 24-hour urine collections. Each stool specimen was assayed for Sr^{85} during the entire study. Starting on the 13th day following intravenous injection of Sr^{85}, 9 g ammonium chloride were given orally per day on 5 consecutive days. Infusions of 500 ml of 5% glucose in water containing 50 ml calcium gluconate (469 mg Ca^{++}) were given daily for a 4-hour period on 3 successive days (study days 15, 16 and 17) so that ammonium chloride and infusions of calcium were given simultaneously for 3 days.

The technic of administration of Sr^{85} and of assaying Sr^{85} plasma levels and urinary and fecal excretions has been previously described(2,3).

Metabolic balances of nitrogen, calcium and phosphorus were determined on aliquots of 6-day pools of urine and stool collections and on aliquots of the diet during the control and experimental studies to ascertain that the metabolic status of the patients remained unchanged at the time the various studies were performed. Nitrogen balances were not determined during the period of ammonium chloride administration.

The diet and excreta were analyzed for nitrogen, calcium and phosphorus on aliquots of each 6-day metabolic pool. Analyses of urinary and fecal nitrogen were performed by the Kjeldahl method, of phosphorus by the method of Fiske and SubbaRow(6) and of urinary calcium by the method of Shohl and Pedley(7). Stool calcium and phosphorus were determined on ashed aliquots of 6-day collection pools.

Results. Fig. 1 illustrates the comparative effect of intravenously administered calcium

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TABLE I. List of Patients Studied.

Patient	Age	Sex	Diagnosis	Studies performed*
1	71	♂	Mild osteoarthritis	Intrav. calcium
2	52	♀	Carcinoma of breast	" "
3	63	♀	Osteoporosis	" "
				" " and oral ammonium chloride
4	77	♀	"	Intrav. calcium
				" " and oral ammonium chloride
5	73	♂	Carcinoma of prostate	Intrav. calcium
				" " and oral ammonium chloride
6	70	♀	Osteoporosis	Intrav. calcium
				" " and oral ammonium chloride

* A tracer dose of Sr^{85} was given intrav. on first day of each study. Intrav. calcium was given for 3 days, starting on study day 15. In studies in which the combination of intrav. calcium and oral ammonium chloride was used, 9 g NH_4Cl were given orally per day for 5 days starting on study day 13.

and of orally administered ammonium chloride on urinary Sr^{85} excretion at the time of Sr^{85} injection. Calcium and ammonium chloride were given singly and in combination in different studies to Patient 1. Urinary Sr^{85} excretion was lowest during low calcium intake. The enhancement of urinary Sr^{85} excretion obtained with intravenously infused calcium or orally administered ammonium chloride was of similar magnitude. A combination of both agents resulted in the greatest increase in Sr^{85} excretion. For comparative purposes, the effect of high calcium intake alone and that of ammonium chloride during high calcium intake on Sr^{85} excretion are also graphed in Fig. 1. During high calcium intake, urinary Sr^{85} excretion was almost as high as during the oral administration of ammonium chloride during low calcium intake. Ammonium chloride, given orally during high calcium intake, resulted in a 10-day cumulative urinary Sr^{85} excretion of similar magnitude to that obtained by the combined use of intravenously administered calcium and orally administered ammonium chloride during low calcium intake.

Fig. 2 shows the effect of infusions of calcium gluconate on urinary Sr^{85} excretion on the 15th, 16th and 17th day following injection of Sr^{85} in 2 patients who were in different states of calcium metabolism. In Patient 1, each calcium infusion considerably increased Sr^{85} excretion. In contrast, the urinary excretion of Sr^{85} of Patient 2 showed irregular fluctuations on the days of calcium infusion and only a slight, if any, increase occurred. Before calcium gluconate was infused, the urinary Sr^{85} excretion of Patient 2 was approximately 3 times and urinary calcium excretion approximately 10 times as high as that of Patient 1. The calciuria of both patients increased on the 3 days of calcium infusion and returned to approximate pre-infusion levels on subsequent days.

Fig. 3 shows the comparative effectiveness of intravenously injected calcium and of orally administered ammonium chloride 2 weeks after injection of the Sr^{85} tracer (Patient 1). The prompt rise of urinary Sr^{85} excretion observed when calcium was infused contrasts with the gradual increase of urinary Sr^{85} excretion when ammonium chloride was given orally for several days. Increased Sr^{85} excretion persisted for 2 to 3 days after discontinuation of ammonium chloride. The 5-day cumulative urinary Sr^{85} excretion (days 15-19) was higher when ammonium chloride was given than following calcium gluconate infusions. The changes in urinary calcium in both studies are shown in the lower half of this graph.

Fig. 4 presents the results obtained with combined use of intravenously infused calcium and orally administered ammonium chloride 2 weeks after injection of the Sr^{85} tracer (Patient 3). A distinct increase in urinary Sr^{85} excretion occurred when calcium gluconate was infused on study days 15, 16

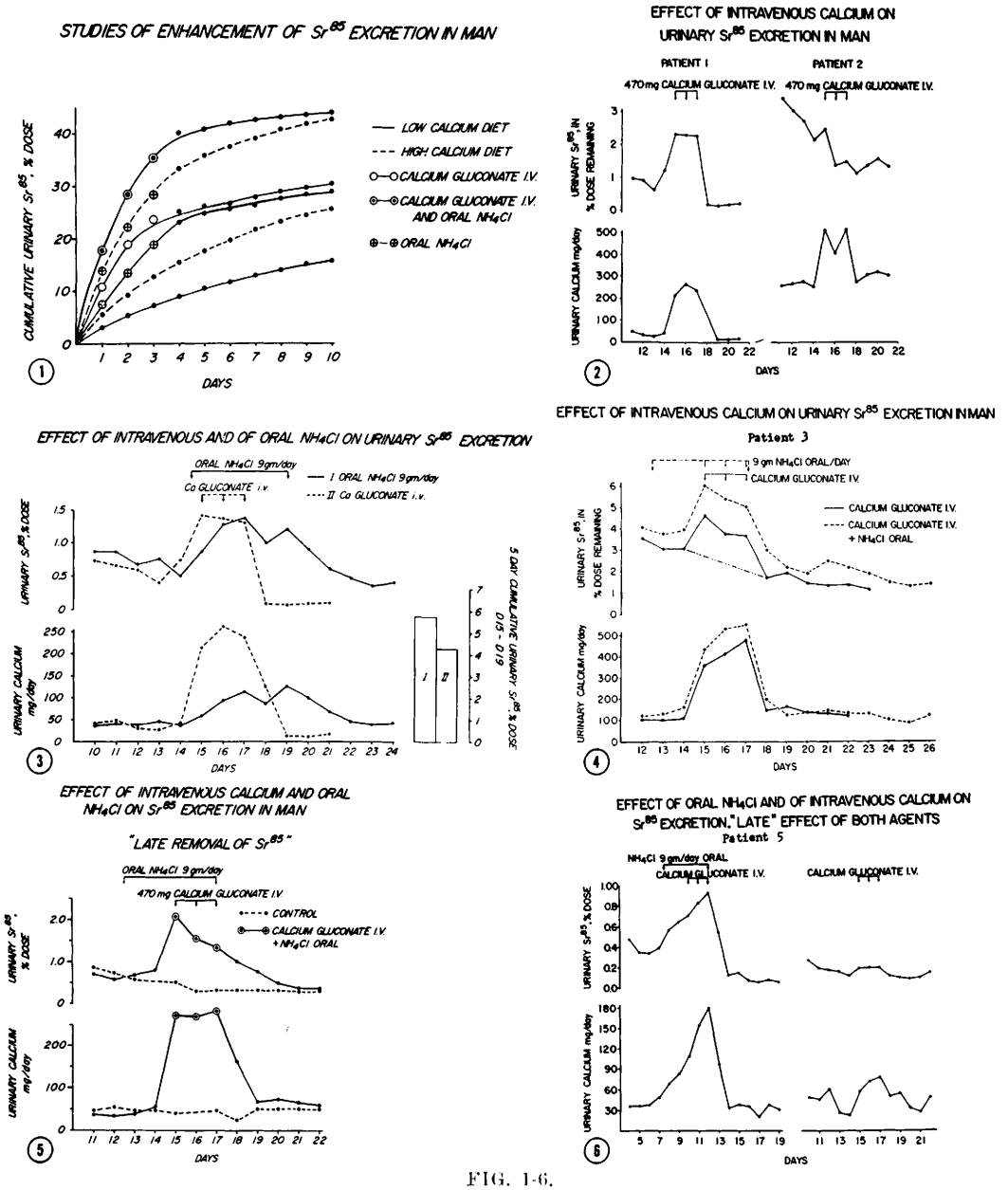

FIG. 1-6.

and 17 (solid line) and urinary Sr^{85} excretion was further increased when ammonium chloride was given simultaneously (dotted line). Before calcium and ammonium chloride were administered, 65.6% of the originally administered dose of Sr^{85} had been excreted. Sr^{85} excretion is therefore expressed in per cent of the administered dose remaining in the body at the time the enhancing agents were administered.

Fig. 5 shows a distinct rise of urinary Sr^{85} excretion when ammonium chloride was given orally and calcium gluconate intravenously to Patient 6. This graph also shows that the elevation of the urinary Sr^{85} excretion persisted for 2-3 days after discontinuation of ammonium chloride.

The contrasting effects obtained in Patient

TABLE II. Effect of Oral NH_4Cl and of Intravenous Calcium on Sr^{85} Excretion in Man (Late Phase).

Patient	Sr^{85}, % dose remaining on day 14		Urinary Sr^{85} excretion, days 15-20, % of dose remaining			Factor of increase (study phase)	
	Control 1	Control 2	Control	Ca gluc.	Ca gluc. + NH_4Cl	Ca gluc.	Ca gluc. + NH_4Cl
1	61.6	—	1.6	7.0	—	4.4	—
2	23.9	—	7.1	7.5	—	none	—
3	34.4	31.7	9.3	14.2	21.1	1.4	2.3
4	41.3	44.6	5.8	11.9	15.0	2.1	2.6
5	90.4	92.3*	.6, 1.0*	.8	4.0*	none	4.0
6	55.4	54.3	5.7	7.5	16.5	1.3	2.9

* Days 8-12 inclusive.

Control 1 = prior to infusion of calcium gluconate.
Control 2 = prior to combined administration of oral NH_4Cl and of intrav. calcium.

5 with calcium infusions and with the combination of intravenously infused calcium and orally administered ammonium chloride are illustrated in Fig. 6. The urinary Sr^{85} and calcium excretions were extremely low in this patient before either agent was given. When calcium gluconate was infused on study days 15, 16 and 17, there was only a very slight and irregular increase of urinary Sr^{85} excretion. However, the combined use of intravenous calcium and oral ammonium chloride led to an approximate 3.5-fold increase of urinary Sr^{85} excretion, which was accompanied by an approximate 6-fold increase of urinary calcium.

Table II shows that the combined use of intravenously injected calcium and orally administered ammonium chloride was more effective in increasing Sr^{85} excretion than infusions of calcium alone. This is best illustrated by the data of Patient 3. There was little, if any, increase in Sr^{85} excretion on the days of the calcium infusions but the use of intravenous calcium together with oral ammonium chloride increased urinary Sr^{85} excretion approximately 4-fold.

Discussion. Very few agents are available for the effective removal of radiostrontium. Changing the calcium/phosphorus ratio of the diet, for instance, either by increasing calcium intake or by drastically decreasing dietary phosphorus, has been shown to reduce the skeletal radiostrontium content in experimental animals(8,9). However, this severe reduction of phosphorus intake led to osteomalacia. Also, this procedure is impractical in man, since severe restriction of phosphorus intake can only be achieved by simultaneous reduction of dietary protein intake. The effect of increased calcium intake has been studied in man and was found to be of limited value in decreasing the absorption of Sr^{85} and increasing its excretion(10,11). Chelating agents are only of limited value in the removal of radiostrontium because of the higher stability constants for calcium than for strontium(12). The use of sodium salts of chelating agents may, in fact, lead to a decrease in radiostrontium excretion(13).

Extensive studies of the removal of radiostrontium from man have been carried out in this laboratory in the past few years. The increase in excretion obtained with ammonium chloride is in agreement with some of the data reported by Hamilton on removal of radiostrontium from rats(14). The absolute amounts of radiostrontium removed from man by ammonium chloride 2 weeks after exposure were small but one has to consider that as much as 50% or more of the administered dose had been excreted by the time the enhancing agents were administered. It is not clear whether the increased radiostrontium excretion in the "late" phase is due to removal of radiostrontium from bone or from soft tissue. It is usually assumed that the major fraction of the retained radiostrontium is deposited in bone in 2 weeks, so that a negligible fraction of the administered dose would be present in soft tissue at that time. Jaffe *et al.* have shown that demineralization of the skeleton can be induced in dogs by the use of ammonium chloride(15). The increase in urinary calcium during administra-

tion of ammonium chloride in the studies reported here indicates that calcium was removed from bone due to acidosis and Sr^{85} may, therefore, also have been concomitantly removed from the skeleton. However, the induced excess of Sr^{85} excretion in man may be in part due to the removal of Sr^{85} from soft tissue rather than from bone, since tissue distribution studies carried out in man with tracer doses of Sr^{85} and Ca^{45} have shown that the soft tissue concentration of Sr^{85} was higher than expected several weeks after injection of the tracer(16).

The studies reported here indicate that the use of ammonium chloride together with intravenously administered calcium is more effective than the use of either agent alone 2 weeks after injection of the tracer. The calcium metabolism of the individual and the percentage of radiostrontium retained in the body at the time of the use of the enhancing agents are decisive factors in increasing Sr^{85} excretion. This is well-illustrated by the contrasting effect obtained with infused calcium in Patients 1 and 2. Although increased calciuria was observed in both patients, the urinary Sr^{85} excretion did not increase in Patient 2 who had both a very high urinary calcium excretion and a high Sr^{85} excretion prior to the calcium infusion. The small percentage of the dose of Sr^{85} which remained in the body at that time may have been inaccessible for removal. In studies in which other agents were used, the increase of Sr^{85} excretion was minimal in persons who had a high urinary calcium and therefore, frequently, also a high urinary radiostrontium excretion(4,5). Similarly, the state of calcium metabolism also played an important role in the failure to increase Sr^{85} excretion by intravenously administered calcium in Patient 5, who had osteoblastic bone metastases and a great tendency to retain calcium. However, the simultaneous use of orally administered ammonium chloride apparently led to active demineralization and to a relatively high excretion of calcium which was accompanied by increased radiostrontium excretion.

Summary. 1. Studies of the removal of radiostrontium (Sr^{85}) from man have been carried out under controlled dietary conditions with the combination of orally administered ammonium chloride and intravenously infused calcium. 2. Each agent alone increased Sr^{85} excretion 2 weeks after administration of the tracer. 3. The use of both agents in combination was more effective in removal of radiostrontium than either agent alone. 4. The effectiveness of either modality of treatment greatly depended on the calcium metabolism of the individual.

1. Spencer, H., Brothers, M., Berger, E., Hart, H. E., Laszlo, D., PROC. SOC. EXP. BIOL. AND MED., 1956, v91, 155.

2. Spencer, H., Laszlo, D., Brothers, M., *J. Clin. Invest.*, 1957, v36, 680.

3. Spencer, H., Samachson, J., Kabakow, B., Laszlo, D., *Clin. Sci.*, 1958, v17, 291.

4. Spencer, H., Feldstein, A., Samachson, J., *Fed. Proc.*, 1960, v19, 351.

5. Spencer, H., Samachson, J., *Clin. Sci.*, 1961, v20, 333.

6. Fiske, C. H., SubbaRow, Y., *J. Biol. Chem.*, 1925, v66, 375.

7. Shohl, A. T., Pedley, G. G., *ibid.*, 1922, v50, 537.

8. Copp, D. H., Kawin, B., Meet. Argonne Nat. Lab., Oct. 1955, ANL-8555.

9. Ray, R. D., *ibid.*

10. Spencer, H., Samachson, J., Laszlo, D., *Fed. Proc.*, 1958, v17, 154.

11. Spencer, H., Li, M., Samachson, J., *J. Clin. Invest.*, 1961, v40, 1339.

12. Schubert, J., *Atompraxis*, 1958, v4, 393.

13. Spencer, H., Samachson, J., Laszlo, D., PROC. SOC. EXP. BIOL. AND MED., 1958, v97, 565.

14. Hamilton, J. G., U. S. A.E.C. Declassified Document MDDC-1142, 1943.

15. Jaffe, H. L., Bodansky, A., Chandler, J. P., *J. Exp. Med.*, 1932, v56, 823.

16. Schulert, A. R., Peets, E. A., Laszlo, D., Spencer, H., Charles, M., Samachson, J., *Internat. J. Appl. Rad. and Isotopes*, 1959, v4, 144.

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