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Effect of Magnesium on Uptake and Retention of Radioactive Strontium.* (29427)

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It has been reported that the feeding of magnesium ions increased the elimination of radioactive strontium by rats that had received the isotope either one or 30 days before treatment(1). Magnesium ion is a potent hypercalciuric agent(2,3) and it was presumed that the increased Sr^{89} elimination via the kidney accompanied the enhanced calcium excretion. This effect of magnesium was evident as late as 30 days after administration of the tracer; similar results have been obtained when Ca^{45} was used as a tracer(4,5). To date, no procedure based on a carrier effect(6) acidosis(7) or chelation(8) has had any effect on the turnover of strontium that had been deposited in bone for any length of time before initiation of treatment. A low phosphorus diet has been shown to decrease uptake of Sr^{89} by the skeleton(9,10) and more recently it was observed that a low-phosphorus diet initiated 3 months after injection of Sr^{90}-Y^{90} into mice did decrease its retention(11). The following studies were designed to investigate further and quantify the effects of Mg^{++} on the removal of "bone-fixed" strontium, since any procedure which could enhance the turnover of skeletal strontium would be of practical importance in treatment of the internal radiation hazard from Sr^{90}. Use of a gamma emitter, Sr^{85} and specialized whole body counting apparatus made possible the direct and repeated *in vivo* measurements of Sr^{85} retention as a function of time following treatment.

Experimental. Rats of the Sprague-Dawley strain were used. In Part I, the groups, labeled young adult rats, had an average weight of 230 g and the groups labeled old adult rats (Groups 8 and 9) weighed ap-

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TABLE I. Effect of Orally-Administered Mg^{++} on Retention of Chronically-Fed Sr^{85}.

Group		No. of rats	Final Sr^{85} retention*(%)	Biological t ½† (days)
		Young adult rats—stock diet		
4	Control	11	60.79 ± .92‡	55.84 + 3.00‡ — 2.71
1	$MgCl_2$ from day 1	10	57.11 ± 1.37	47.98 + 2.15 — 1.43
3	$MgCl_2$ from day 31	10	56.10 ± .79	47.45 + 2.15 — 1.96
		Young adult rats—low Ca diet		
6	Control	10	60.04 ± 1.02	57.20 + 3.94 — 3.47
5	$MgCl_2$ from day 31	9	54.69 ± 1.56	46.98 + 2.09 — 1.92
		Old adult rats—stock diet		
9	Control	13	61.45 ± 1.15	58.48 + 6.02 — 5.00
8	$MgCl_2$ from day 31	13	57.92 ± .72	50.53 + 3.89 — 3.38

* Retention at day 72 expressed in % of day 34 value.
† Days 34 to 72.
‡ Standard error of estimate.

proximately 340 g. The Sr^{85} Cl_2 was carrier free and mixed in the diet at a level calculated to give a 27 day retention of approximately 1 μc. $MgCl_2 \cdot 6H_2O$ (0.2 meq/ml) was added to the drinking water and administered to the animals concurrently with the feeding of the Sr^{85} labeled diet for 27 days. Groups 3, 5, 8 received the $MgCl_2$ drinking water for 41 days after an initial 27 day feeding of the labeled diet. Groups 4, 6 and 9 were comparative controls. All groups were fed stock diet except Groups 5 and 6 which were fed a low Ca diet (Table I). All control animals received 9% dextrose solution as drinking water.

In Part II, the animals weighed an average of 80 g at time of injection. Each rat was injected with 1.5 μc of Sr^{85} intraperitoneally and was given $MgCl_2$ either at 8 or 28 days after the isotope injection.

Whole body retention of Sr^{85} was determined *in vivo* using a scintillation detector. The animals were positioned at a fixed geometry in a glass tube over a shielded 2.5″ Na I (Tl) crystal. A single channel pulse height analyzer was used to measure the counts in the Sr^{85} photopeak with appropriate correction for background.

Results and discussion. The uptake and retention of Sr^{85} in Groups 1, 3, and 4 during the 27 day feeding of labeled diet and for an additional 41 days on unlabeled stock diet are shown in Fig. 1. It is evident that Group 1, which received $MgCl_2$ in its drinking water from the outset, took up and retained approximately 50% of the Sr^{85} of the controls (Group 4) or of Group 3 which did not receive the $MgCl_2$ until day 31. Groups 5 and 6 on the low Ca diet had double the uptake and retention of the rats on the stock diet.

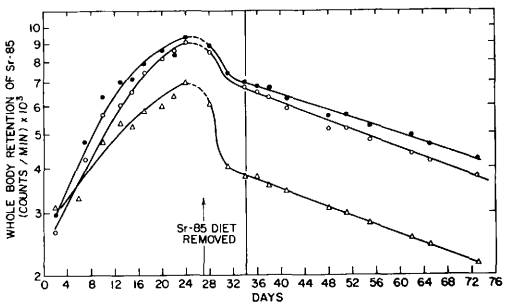

FIG 1. △ Refers to Group I; ○ refers to Group III; ● refers to Group IV.

The mechanism of action of Mg^{++} in decreasing the skeletal uptake of Sr^{85} is not known. It has been shown that Mg^{++} increases markedly the urinary calcium(2-4) and that this ion has a direct effect on the kidney(1,12). Since strontium is handled by

the animal in a manner somewhat similar to that of calcium, it is not surprising that magnesium also enhances urinary strontium. It is also possible that Mg^{++} may compete with Sr^{++} for available adsorption sites on the crystal surface of bone since it appears to be a surface limited ion. However, this alternative is not too likely since it has been reported that the continued administration of magnesium does not increase its deposition in bone(13).

The retention of Sr^{85} at 72 days after the labeled diet, when expressed in terms of the 34 day value (100% "bone-fixed" Sr^{85}), is shown in Table I. The final retention of the control groups (Groups 4, 6 and 9) was very similar (60.04 to 61.45%). The Mg^{++} treated groups (1, 3, 5 and 8) all had mean Sr^{85} retentions lower than their respective controls. An analysis of variance indicated that their differences were statistically different at days 10, 15, 20 and 23 ($p<.01$). The mean Sr^{85} retention of Groups 3, 5 and 8 which received the Mg^{++} on day 31, all had approximately the same mean retention value. Thus, the low calcium diet in Groups 5 and 6 appeared to have no effect on the action of Mg^{++}.

A more sensitive comparison between the groups fed Mg^{++} and their controls is provided by comparing the slopes of the exponential retention curves of the various groups. This technique utilizes all the data collected over the 38 day period and involves the computer derived linear least squares fit of these data. The slopes expressed as biological half times are shown in Table I for all the groups. Again, in every group fed Mg^{++}, a shorter mean biological half time results when compared to the corresponding controls. The differences between the means are small but statistically significant. The differences in slope also suggest that the effect of Mg^{++}, small as it is, increases with prolonged administration.

Since Mg^{++} was administered within a day after cessation of the feeding of the labeled diet, an effect of Mg^{++} on the skeletally bound Sr^{85} was still not established with certainty since Mg^{++} could be affecting the Sr^{85} retained in the GI tract or in the soft tissues. Therefore, in part 2 of this experiment (Table II), groups of rats were fed Mg^{++} beginning at both 8 and 28 days after they were injected intraperitoneally with Sr^{85}. This lapse of time was to insure that relatively all the Sr^{85} in the body was in the skeleton. The mean values for Sr^{85} retention over 15 days in Group 11 (fed Mg^{++} at 8 days after Sr^{85}) are shown in Table II. At one day after commencement of oral Mg^{++}, a slight drop in the mean retention of Group 11 occurs as compared to the control, Group 12. For the next 15 days, the mean retention of the group fed Mg^{++} remained slightly lower than that of the control group. If 28 days are allowed to elapse between Sr^{85} injection and Mg^{++} administration, the effect on Sr^{85} turnover is even less marked than after 8 days. After 15 days of feeding Mg^{++}, the mean retention of the treated group (Group 13) is 4% lower than that of the control group.

TABLE II. Effect of Orally-Administered Mg^{++} on Turnover Rate of Injected Sr^{85}.

Group	No. of rats	Final Sr^{85} retention,* day 15 (%)	Biological $t_{1/2}$† (days)
Control (10)	9	65.37 ± .99‡	26.36 + 1.64 — 1.45
Mg^{++} fed§ (11)	9	58.39 ±1.06	22.85 + 2.34 — 1.95
Control (12)	9	72.43 ± .81	35.64 + 2.60 — 2.27
Mg^{++} fed‖ (13)	9	69.64 ± .59	31.54 + 1.55 — 1.41

* Retention at 15 days expressed in % of initial injected value.
† Days 1-15.
‡ Standard error of estimate.
§ Group fed Mg^{++} 8 days after I.P. injection of Sr^{85}.
‖ Group fed Mg^{++} 28 days after I.P. injection of Sr^{85}.

It is clear, therefore, that the effect of magnesium ions on the turnover of skeletal Sr^{85} in the body is slight but statistically significant; this is particularly true if the Sr^{85} is well fixed in the skeleton, *i.e.*, 8 or 28 days after injection. As a practical approach to dealing with Sr^{90} contamination in the population, the simultaneous administration of Mg^{++} along with Sr^{90} contaminated food could be of value. Clinical studies have shown

that man can tolerate relatively large amounts of Mg^{++} for prolonged periods without ill effect(14). It should be mentioned that other than an initial weight loss and early diarrhea no gross clinical effects were observed in these rats. However, once radioactive strontium is fixed in the skeleton, the possibility of enhancing its turnover rate is small.

Although it would appear obvious, it should be emphasized that, although agents may cause significantly greater urinary and fecal excretion of skeletally bound isotope, unless a major portion of the skeleton turns over, this increased excretion will result in only a minor change in the skeletal burden of strontium.

Summary. Administration of Mg^{++} concurrently with radioactive strontium decreased significantly skeletal retention of the isotope. Mg^{++} administration had a small but significant lowering effect on the retention of radioactive strontium when administered after the isotope was well fixed in bone.

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Antigen Pretreatment and Mechanisms of the Resulting Temporary Tolerance.* (29428)

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In previously reported studies antigen pretreatment was evaluated as a technique for prolonging the survival of homografted kidneys in dogs(1,2). Two cc donor blood given 10 and 5 days before transplantation, was found to be of moderate effectiveness, allowing a functioning survival of 29.2 ± 10.9 days (controls 9.1 ± 1.3 days). Recipients thus conditioned demonstrated a clinical "wasting syndrome" characterized by anorexia, vomiting, diarrhea, weight loss, anemia and a persistent leukocytosis beginning long before renal function deteriorated. At autopsy they all showed severe depletion of lymphocytes in the spleen and lymph nodes. The thymus, however, was uniformly spared. The present studies were an attempt to answer several questions arising from the above work: 1. Is a graft-*vs*-host reaction involved in the genesis of this lymphoid depletion and delayed rejection? 2. Is the spared thymus a source of, or stimulus to, lymphocytes re-populating these depleted animals? 3. Does the source or bulk of the transplanted allogeneic tissue affect lymphoid depletion?

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