uracil has practically attained a diffusion equilibrium in this time. Similar results were obtained with thymine and fluorouracil. Because of the rapidity of entrance into the cells at 39°C it was difficult to measure accurately the k_p for these compounds. However, one can estimate from the experiments that the k_p's at 39°C fall in the range 10^{-3} to 10^{-4} cm/min.

Schanker and Tocco(8) have reported studies on intestinal absorption of uracil and thymine which they interpret as evidence for an active transport of these compounds. If the cells of the intestinal epithelium have as high a permeability to these compounds as do the Ehrlich ascites cells, an active transport would be unlikely. In that case, their findings might be explained by a high permeability for thymine and uracil and a saturation of metabolic pathways with increasing concentration.

Summary. Uracil, thymine and fluorouracil enter Ehrlich ascites cells by diffusion. The permeability constants at 5°C were $1.2 \cdot 10^{-5}$ cm/min for uracil, $3.2 \cdot 10^{-5}$ cm/min for thymine and $1.1 \cdot 10^{-5}$ cm/min for fluorouracil. Accurate measurements could not be obtained at 39°C because of the rapidity of the equilibration of the intracellular space but estimates of 10^{-3} to 10^{-4} cm/min for the permeability constants at 39°C were obtained.

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Effect of Magnesium Ions on Removal of Radiostrontium from Rats.* (27127)

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In recent years the fear of increased dietary contamination with radioactive Sr-90 from "fall-out" has stimulated considerable effort towards finding a safe and effective means of decreasing the body burden of radioactivity. Different experimental approaches have been utilized in the search, *i.e.*, chelating agents(1); alterations in salt content of the diet(2); dilution with non-radioactive carrier(3); the acidotic salt NH_4 Cl (4); and Vit. D_3(5). Relatively toxic amounts of some of these substances, *i.e.*, Vit. D and NH_4 Cl, must be administered to be effective. A certain degree of success has been obtained by increasing the calcium content of the diet, depending on how soon after ingestion of isotope the dietary change was made(3). In general, chelating agents have proven unsatisfactory following chronic ingestion of isotope(6).

Magnesium ion, a potent hypercalciuric agent(7,8), recently has been shown to increase urinary Ca-45 regardless of whether the nuclide was ingested one or 60 days before(9). Since strontium resembles calcium in its affinity for bone and in its elimination from the body, magnesium was tested for its ability to increase the elimination of radioactive strontium by rats. The following experiments demonstrate that oral or parenteral ad-

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TABLE I. Relative Excretion of Strontium[89].* (Rats 200-240 g)

Treatment (single dose)	Hours 0–8	8–24	0–24
Control	100	100	100
Beryllium (.43 meq)	265	69	131
Magnesium (")	521	130	237†
Calcium (")	193	79	117
Strontium (")	324	111	184†
Barium (")	36	All dead	—

No food—only glucose.
* Strontium[89] administered 30 days before.
† Statistically significant—P = <.001.

ministration of magnesium ions significantly increases the elimination of strontium by rats which had received Sr-89 either one or 30 days before.

Experiment. Male rats of the Holtzman strain were used in all experiments. In the short-term experiments, rats received 10 μc of Sr-89 intraperitoneally 48 hours before the different treatments were initiated. In the experiments in which treatment was begun 30 days after Sr-89 ingestion, the animals received 100 μc of Sr-89 intraperitoneally. The animals were maintained on 10% glucose in their drinking water to insure an adequate volume of urine and caloric intake. In the experiment in which Mg Cl_2-H_2O was given orally, it was incorporated in the 10% glucose drinking water at a level of 0.2 meq. magnesium per ml. In all other experiments, unless otherwise noted, the animals received subcutaneous injections of 0.86 meq. of Mg SO_4-$7H_2O$ per 100 g body weight, or 0.86 meq. citrate per 100 g body weight or 0.5 mg Prednisolone per 100 g body weight. The feces after ashing and dissolution in dilute HNO_3 were plated out in stainless steel planchets, as were aliquots of urine, and counted with a thin window, proportional flow-gas counter. The usual corrections for decay and background were made.

Results. Effect of elements of Group II of the Periodic Table. Subcutaneous administration of most elements of Group II of the Periodic Table (Table I) increased urinary elimination of Sr-89 by adult rats of 60 to 70 days of age which received a single injection of the isotope 30 days before. However, only magnesium and strontium significantly increased urinary Sr-89 during the 0-24 hour period. The rats which received barium died within 24 hours and those which received beryllium died within a week.

Effects of combinations of magnesium with other hypercalciuric agents on urinary Sr-89 by adult and young rats. Citrate(10) and Prednisolone(11), if administered to rats, cause hypercalciuria and also increase urinary Ca-45 which had been deposited 60 days before(9). However, neither of these agents was capable of augmenting the effect of magnesium ion alone on elimination of Sr-89 by adult rats of 50 to 60 days of age (Table II). If anything, these materials, singly or in combination, depressed the action of magnesium.

During the 0-8 hour collection period, citrate and magnesium, but not Prednisolone, effectively increased the elimination of the isotope (Table III) by young rats of 30 to 35 days of age which had received Sr-89 forty-eight hours before. During the 8-24 hour interval, no effect was observed. Again, combinations were no more effective than

TABLE II. Relative Excretion of Strontium[89].† (Rats 175-225 g)

Treatment	Hours 0–8	8–24	Sum 0–24
Control	100	100	100
Magnesium	376	138	309*
Citrate	140	114	133
Prednisolone	142	76	124
Mg + citrate	159	155	158
Mg + Prednisolone	256	167	231*
Citrate + Prednisolone	45	117	65
Mg + citrate + Prednisolone	197	181	193*

* Significantly different from controls.
† Strontium[89] administered 30 days before.

TABLE III. Percent of Dose Excreted. (Rats 90-100 g)

Treatment (single dose)	Hours 0–8	8–24	Sum 0–24 (Urine)	0–24 Feces
Control	.48	.34	.82	2.5
Magnesium	.97*	.35	1.32*	2.7
Citrate	.76*	.29	1.05	2.6
Mg + citrate	1.05*	.32	1.37*	2.5
Prednisolone	.40	.27	.67	2.6
Mg + Prednisolone	1.04*	.33	1.37*	2.4
Idem + citrate	1.13*	.11	1.24	3.0

* Significantly different from controls.

TABLE IV. Percent of Dose Excreted. (Rats 200-250 g)

Treatment (4 doses)	Hours 0–48 Urines	0–48 Feces	Sum
Control	.46	3.79	4.3
Magnesium	2.89*	3.81	6.7
Citrate	.91*	3.83	4.7
Mg + citrate	2.71*	3.05	5.8
Prednisolone	.41	3.54	3.9
Mg + Prednisolone	1.87*	3.37	5.2
Mg + citrate + Prednisolone	1.86*	3.05	4.9

* Significantly different from controls.
Dose at zero time, 19 hr, 25 hr, 43 hr.

magnesium alone and no significant effect on fecal Sr-89 was noted.

When these substances were administered in divided doses to adult rats of 60 to 70 days of age which had received the isotope 48 hours before (Table IV), essentially similar results were obtained; namely, magnesium was more effective alone than in combination with citrate or Prednisolone or both.

Effect of oral administration of Mg Cl_2-H_2O on Sr-89 excretion. Oral administration of magnesium salts to rats fed a stock or calcium-free diet also increased urinary Sr-89 (Table V). In this experiment, substitution of a low calcium diet for the stock diet did not affect the urinary Sr-89 significantly. Fecal Sr-89, however, was decreased following oral administration of magnesium (Table VI). This was not seen after subcutaneous administration of magnesium (Tables III and IV). However, there was a net increased excretion of isotope of 23% by the rats on stock diet and of 29% by the rats on the calcium-free diet following the 12 day oral administration of Mg Cl_2-H_2O.

Discussion. These studies have demonstrated that magnesium ion may be a useful adjunct to the other agents commonly used for increasing the elimination of radioactive strontium from animals. Magnesium is relatively non-toxic and may be administered to man or animals over long periods of time, provided there is an adequate supply of calcium and especially phosphorus in the diet. Continued administration of magnesium to animals does not increase the bone content of this element(12), since it is believed to be attached only on the surface of the bone(13). Moreover, since this element has such a rapid action in mobilizing calcium from bone, it could be of use in conditions where an immediate increase in serum calcium is needed.

Although it has been reported that the inhibition of Sr-89 deposition in bone by the oral administration of Mg SO_4 results from the action of sulfate ion precipitating Sr-89 in the gastrointestinal tract(14), comparison of different sulfates in causing hypercalciuria have shown that magnesium ion and not sulfate ion is primarily responsible for this action(9). Moreover, in the present experiments, oral administration of Mg Cl_2-H_2O was also effective in increasing urinary Sr-89.

TABLE VI. Total Counts Excreted in Feces.

	Days 1–4	5–8	9–12	Sum
A. Stock diet				
Controls	48,000	24,000	27,000	99,000
Magnesium	30,000	16,000	14,000	60,000
B. Low calcium diet				
Controls	68,000	30,000	22,000	120,000
Magnesium	53,000	20,000	21,000	93,000

The conditions in these experiments are unlike those where animals or man consume a constant daily intake of a radioactive nuclide. As pointed out by Wasserman and Comar(6), extrapolations of a single dose experiment to man or to other experimental conditions may be dangerous. Nevertheless, it is not too unreasonable to expect that mag-

TABLE V. Total Counts Excreted in Urine.

		Days 1 + 2	3 + 4	5 + 6	7 + 8	9 + 10	11 + 12	Sum
A. Stock diet	Controls	20,000	20,000	11,000	11,000	12,000	13,000	87,000
	Magnesium	27,000	33,000	28,000	20,000	36,000	36,000	177,000
B. Low calcium diet	Controls	19,000	16,000	13,000	12,000	11,000	11,000	82,000
	Magnesium	38,000	29,000	33,000	32,000	31,000	30,000	193,000

nesium might be beneficial even in cases of chronically ingested Sr-90, since it was effective in animals on a normal diet. Furthermore, it was effective in increasing elimination of the Sr-89 which had been administered to the rats 48 hours or 30 days before. Moreover, its mechanism of action appears to be quite different from that of other agents that increase Sr-89 elimination. In the studies concerned with decreasing bone uptake and increasing excretion by the use of excessive calcium or unlabeled strontium in the diet, the mechanism of their action seems to be by a dilution effect(1,2,3). Citrate or EDTA presumably acts as chelating agent (1). Magnesium has no chelating power and although it is a member of the same group of the Periodic Table as calcium and strontium, it has no marked affinity for bone(13). Physiologically, it acts as an antagonist to calcium(15). Using the technic of peritoneal lavage, Talmage has shown that magnesium had no direct action on bone, but does act on the kidney to increase urinary calcium (personal communication). Further evidence for a renal action of magnesium is the immediate hypercalciuria following injection of magnesium ions directly into the renal arteries of dogs (unpublished results). These results are contrary to previous interpretations of the mechanism of action of magnesium in producing hypercalciuria(9). Thus the action of magnesium in promoting increased Sr-89 and Ca-45 elimination appears to be by opening the renal flood gates for calcium and materials similar to it. The increase in urinary Sr-89 observed in these experiments must come from the "older" fraction of bone, *i.e.*, bone that had been formed sometime in the past and not currently being synthesized, since Sr-89 that had been deposited 30 days before was readily eliminated (Tables I and II). Similar findings have been observed following administration of parathyroid extracts to rats(9,16,17). It is possible that regardless of the mechanism producing hypercalciuria, as for example direct action on bone by parathyroid extract or a renal action with magnesium, the bone that had been formed sometime in the past acts as a reservoir of available mineral. This reservoir is very likely the trabeculae as suggested by Bauer *et al.*(18).

The decreased fecal excretion of Sr-89 after oral administration of magnesium is at present inexplicable. It might be expected that an excess of magnesium in the diet might interfere with intestinal absorption of calcium or strontium and thereby cause an increase in fecal calcium and similarly strontium, since it has been reported that magnesium inhibits the active transport of calcium *in vitro* across the intestinal wall(19).

Summary. Magnesium is effective in increasing the elimination of Sr-89 by rats which had been given the isotope either one or 30 days before treatment. It is effective when given orally or parenterally. Oral administration of magnesium decreases fecal Sr-89; however, the sum of urinary and fecal Sr-89 is significantly greater than those of control animals. Supplementation of magnesium with citrate ions or Prednisolone was no more effective than magnesium alone.

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Role of Vitamin A in Induction of Vitamin K Deficiency in the Rat.* (27128)

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It has been recognized since 1944(1) that hypervitaminosis A in the rat leads to hemorrhages and hypothrombinemia which can be prevented by administration of Vit. K(1,2). The amounts of Vit. A used were many times the amount required for maintenance of the experimental animals.

Our interest in the possible effects of smaller amounts of Vit. A in development of symptoms of Vit. K deficiency in the rat arose from data obtained with 2 diets similar in all respects except for the levels of several micronutrients. The basic diet contained cooked ground beef and had been used by Metta *et al.*(3) in their original observation of its hemorrhagenic effect in male rats. Some modification in our hands gave a diet which produced little evidence of a coagulation defect. The difference in supplemental levels of Vit. A seemed most significant.

In view of the speculation concerning the biological role for Vit. A acid(4), the effect of this compound in induction of hemorrhage was also studied.

Methods. Rats of the St. Louis University colony were individually caged in suspended one-half inch mesh stainless wire cages and given sufficient fresh diet at either 2- or 3-day intervals to allow *ad libitum* feeding. Ten animals were used in each experimental group. Samples of blood were taken by cardiac puncture under light ether anesthesia and the plasma examined by the viper venom procedure of Hjort *et al.*(5). Although the method may detect changes in concentration of both prothrombin and Stuart factor(6,7), data are given here as the per cent of normal prothrombin concentration. Frozen aliquots of pooled plasma from male rats maintained on Purina laboratory chow were used as normal controls and were assayed with each group of experimental samples. Any value less than 85% of the value for normal controls was taken as indicative of experimentally induced hypoprothrombinemia.† The average and range of observations and number of normal animals (prothrombin concentration greater than 85% of normal) found among the total examined are given as criteria of the effect of the diet. Evidence of spontaneous hemorrhagic death is recorded, but other causes of death or loss such as cardiac puncture are not indicated.

In earlier experiments a feeding duration of 8 weeks was used beginning with weanling rats. Subsequently we devised a more convenient assay for potentially hemorrhagenic diets using adult animals 13 weeks of age. As Mellette and Leone(8) have reported, these animals were more susceptible so that a feeding duration of only 2 weeks reflected the nutritional adequacy of the diet. Samples of cardiac blood were taken for analysis after one and 2 weeks on the experimental ration.

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† This value is based on examination of the plasma of 45 adult male rats maintained in the colony on Purina laboratory chow; mean concentration of prothrombin was 99.4 ± 7.5 (s. d.) % of the pooled plasma control.