MAGNESIUM TURNOVER IN THE HUMAN STUDIED WITH Mg^{28} *

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Despite the relatively large amounts of magnesium present in the cells of most mammals, its *in vivo* functions in man remain poorly defined, a point which is emphasized in a recent review by Wacker and Vallee (1). There is evidence, which is still equivocal, that abnormalities of magnesium metabolism may be involved in several disease states including atherosclerosis (2), myxedema (3), hyperthyroidism (4), acute alcoholism (5), and possibly other conditions (6). Although Wacker and Vallee emphasized that, in view of its established capacity to function as an activator for many *in vitro* enzyme systems magnesium must play a significant role in intracellular metabolic activity, one of the intriguing aspects of magnesium has been its apparently relative inertness—particularly striking when compared with the other major ions in the body. Study of magnesium has been aided by the advent of the isotope Mg^{28} (7), although some caution has been necessary in using this isotope as well as in interpreting results obtained with it because of the relatively low specific activity which has been attained. With these limitations in mind we have made studies that tend to confirm earlier data arrived at by nonisotopic techniques, namely, that there are several relatively small, rapidly equilibrating compartments and one or more in which turnover is very slow. These data on man suggest that there are at least three compartments in the body pool of magnesium turning over with half-times of 1, 3, and 14 to 35 hours, respectively, but that probably 25 to 50 per cent of the magnesium has a turnover rate of less than 2 per cent per day.

MATERIALS AND METHODS

Clinical data. The 10 white adults—3 males of 45, 55 and 62 years of age, and 7 females aged 38, 46, 52, 53, 55, 64 and 72 years—were studied on the metabolic wards of the Hospital of the Brookhaven Medical Research Center for several months or more during the period of these investigations. All but the male aged 55 suffered from hypertension. Since the present observations are not clearly relevant to hypertension, only clinical data which might be pertinent to the present study are mentioned. The male of 55 had had classical rheumatoid arthritis of 3 years' duration but no other disease. The male of 62, who had a history of syphilis, was found to have positive serological tests for syphilis; the root of the ascending aorta was somewhat dilated by X-ray and a Grade I aortic diastolic murmur was present. In view of these findings, a diagnosis of luetic aortitis was made in addition to his undoubted essential hypertension of long standing. The remaining 8 patients had classical essential hypertension. In some patients cardiac enlargement was shown to be present by X-ray, and mild to moderate myocardial damage was evidenced by electrocardiographic changes; however, none had signs or symptoms, present or past, suggestive of heart failure. None of the patients gave a history of renal disease, and renal function studies including intravenous urograms were normal. All of the hypertensive subjects had negative Regitine tests for pheochromocytoma.

During the 8 day period, ranging from 5 days before to 3 days after administration of isotope, the patients were on a constant diet; although this was not identical from patient to patient, it was unvarying for any one patient, so that the magnesium content was fixed at about 50 to 60 mEq per day for each patient. All subjects had been on controlled dietary intakes previous to this study, with each diet calculated and weighed every day. Admission weight was maintained throughout hospitalization. Water intake was unrestricted although measured.

Methods. The isotope Mg^{28}, with a half-life of 21.3 hours, was obtained from the Brookhaven graphite reactor, and after appropriate purification and precipitation as $Mg^{28}(OH)_2$, was neutralized to pH 7.4 with HCl.[1] The highest specific activity that could be obtained ranged from 0.07 to 0.12 μc per mg of Mg^{++}, so that no carrier was added during administration or handling thereafter. After sterilization in an autoclave, the isotope was diluted with 5 per cent dextrose in water to a suitable volume, and delivered intravenously or orally to the patients from a calibrated 100 ml buret, in amounts ranging from 20 to 104 μc in total volumes ranging from 25 to 100 ml. The nonradioactive Mg^{++} infused intravenously ranged from 25 to 80 mEq and slow administration of the fluid was necessary to prevent toxic symptoms from the magnesium:

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[1] The authors are indebted to Mr. H. O. Banks for the chemical preparation of the isotope.

flushing of the face was seen, and subjective feelings of heat in the face, feet, and lower abdominal and genital areas were complained of if the flow rate was too fast; no fall in blood pressure or change in reflexes occurred. Initial calculations indicated that the largest amount of isotope infused, assuming complete decay and no excretion, would give a maximal dose of slightly less than 0.3 rad whole-body irradiation. In light of the actual excretion data, the calculated radiation received may be decreased by approximately a quarter for the isotope administered intravenously.

Urine collections were made in chemically clean bottles; after the volume was measured, aliquots were removed, preserved with H_2SO_4 and stored at room temperature. Stools were similarly collected, homogenized with H_2SO_4, and an aliquot removed for digestion and hydrolysis according to the method of Wallace, Holliday, Cushman and Elkinton (8). Magnesium was measured with minor modifications by the micro-method of Karrman and Borgström (9), a method that was reproducible and accurate as indicated by the following data: *a*) standard solutions containing 10 μg Mg^{++} were titrated with each series of urine or plasma analyses and a random sampling of 40 such standards, extending over the course of these studies, gave a mean recovery value of 10.00 μg (SD $\pm$ 0.203); *b*) analysis of 10 replicates of a pooled plasma sample gave an average of 1.885 mEq per L (SD $\pm$ 0.046), a value in good agreement with the results of others (9–11); *c*) to 3 series, each of 5 aliquots of this pooled plasma, the addition of 10, 20, and 40 μg Mg^{++} resulted in average recoveries of 99.1, 103.2 and 102.2 per cent, respectively. Radioactivity was measured with a well-type NaI scintillation crystal and standard scaler; duplicate 4 ml samples were counted sufficiently to make the counting error 1 per cent or less. In calculating the fraction of the total body Mg which had exchanged with the isotope, allowance was made for urinary or stool loss up to that time as well as for the Mg^{++} infused with the isotope.

RESULTS

Excretion of Mg^{++}

1. After oral administration. Two hypertensive subjects were given 80 μc Mg^{28} orally after which urine collections were made at intervals until the amount of radioactivity found was not significantly above background—about 60 hours later. All stools passed after the ingestion of the isotope were analyzed similarly. Plasma samples were counted at 2, 4, 15 and 39 hours after ingestion; these samples had maximal activity (corrected for decay) in the 15 hour samples. Because plasma activity was of such a low order in all samples—ranging from slightly over twice to a maximum of three times background—the curve of plasma activity has not been shown in Figure 1, which depicts only the urinary and stool excretion of the isotope. It is apparent that gastrointestinal absorption of magnesium was very limited in these two subjects, for in contrast to the results following intravenous administration described in the paragraph below, less than 3 per cent of the isotope was excreted in the urine in 60 hours, while between 10 and 20 times this fraction was found in the stools.

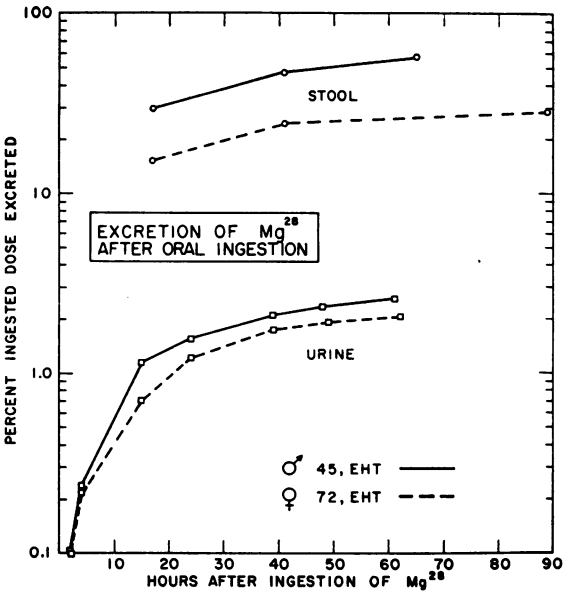

FIG. 1. STOOL AND URINE EXCRETION OF Mg^{28} AFTER ORAL ADMINISTRATION IN TWO PATIENTS WITH ESSENTIAL HYPERTENSION (EHT).

2. After intravenous administration. The data on nine subjects, including the nonhypertensive individual, are shown graphically in Figure 2. In contrast to the preceding study, excretion was virtually confined to the urine: 35 to 50 per cent of the radioactivity appeared in the urine before the isotope decayed to background levels, and in no instance did the stool account for more than about 1 per cent of the injected radioactivity (0.0 to 1.1 per cent). Approximately 25 per cent of the total radioactivity was found in the urines collected between two and five hours after injection of the isotope, values very similar to those found by Brandt, Glaser and Jones (12) for dogs after intravenous administration of this isotope.

The rapid urinary loss of the isotope after intravenous administration was mirrored in a rapid decline in counting rates of the plasma. The low concentration of magnesium in plasma in association with the relatively low specific activity of this

isotope combined to make data based on plasma counting unsuitable for accurate estimation of the time required for establishing equilibrium between tissues and isotope. Approximately 40 hours after intravenous administration the level of plasma activity was so low as to preclude further counting, and at this time equilibrium between tissues and isotope quite evidently had not yet been attained.

"Exchangeable" Mg^{++}

The concentration of Mg^{++} in the urine (2 to 10 × plasma) resulted in higher counting rates than was the case with plasma. The specific activities of the urinary Mg^{++} were used to calculate the "exchangeable" Mg^{++} data shown in Figure 3. Although in several instances the data suggest that exchange between isotopic and tissue Mg^{++} had reached a plateau level, in most instances this was not attained.

About 40 to 50 per cent of the injected dose of Mg^{28} was recovered in the urine during the first 48 hours after administration of the isotope, and only slightly more was recovered in two studies which could be continued for about 90 hours. Graphical analysis (13) of the urinary Mg^{28} curves in terms of exponential components (Figure 4) typically yielded a slow component of 14 to 38 hours half-time, accounting for 10 to 15 per cent of the injected dose, and two more rapid components with one and three hour half-times, respectively, each accounting for 15 to 25 per cent of the injected dose. The sum of the quantities of Mg^{28} accounted for by integration of the components is about 10 per cent greater than the quantity actually recovered because of extrapolation beyond the last measurement. A few additional per cents of the administered dose were found in the stools. Even so, the total accounted for is typically only 50 to 75 per cent of the quantity injected. This indicates that there is at least one slow component not seen in the present data, and that 25 to 50 per cent of the magnesium in the body has a turnover rate of less than 2 per cent per day. It is important to recall that these turnover rates were arrived at in patients receiving magnesium both from the diet and from the low specific ac-

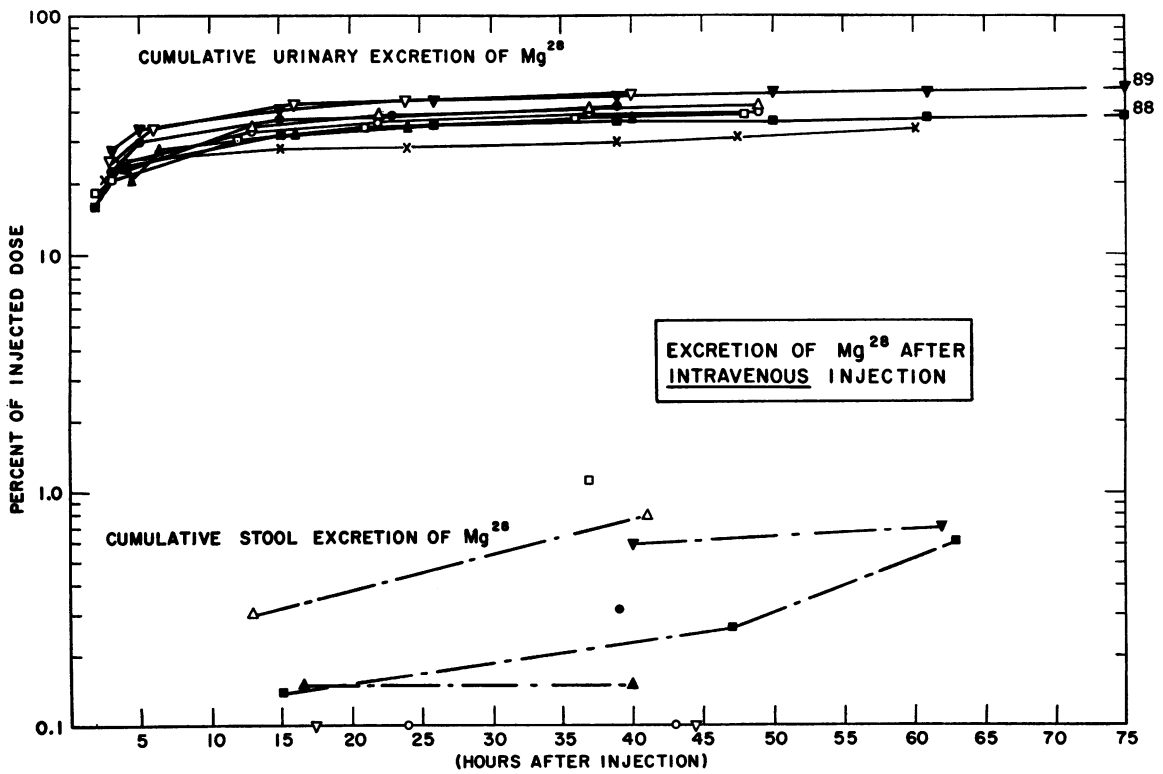

FIG. 2. STOOL AND URINE EXCRETION OF Mg^{28} AFTER INTRAVENOUS ADMINISTRATION IN NINE PATIENTS. Stools were not obtained on one patient.

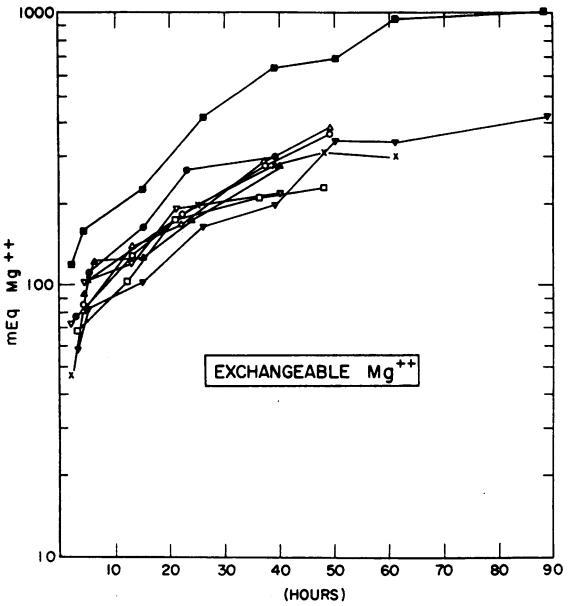

FIG. 3. CUMULATIVE ESTIMATE OF TOTAL EXCHANGEABLE MAGNESIUM AFTER INTRAVENOUS ADMINISTRATION OF Mg^{28} TO NINE PATIENTS.

tivity Mg^{28}. (The amount of magnesium injected was of the same order as that consumed on the constant diet in one day.) It is possible that the true turnover rates are much lower under conditions when lesser amounts of magnesium are being absorbed.

The data on Mg^{++} content of the human from whole body analysis are rather limited, but the estimates of Duckworth and Warnock (14), Forbes, Mitchell and Cooper (15) and Widdowson, McCance and Spray (16) are in rather good agreement, with values amounting to about 30 to 35 mEq per kg of body weight. Shohl's figures (17) are somewhat lower and it has been suggested that this was because of the limitation of the analytical method used for magnesium (16). In Table I are shown the values for exchangeable magnesium on the nine individuals in the present study; in only one of these patients was a value in excess of 10 mEq per kg obtained. It is of interest that five of the hypertensive subjects had values of 3.6 mEq per kg upon completion of the study, suggesting the interesting possibility that a biological invariant was being measured. These data may be interpreted to indicate that up to about 40 to 60 hours, perhaps 10 to 25 per cent of the tissue Mg had come into equilibrium with the isotope. The experiments which were extended for 88 and 89 hours in two individuals may have measured a third of the total body Mg^{++}.

DISCUSSION

Much of the early literature on the absorption and excretion of Mg was reviewed in Mendel and Benedict's paper (18) which appeared in 1909. Although there were considerable differences

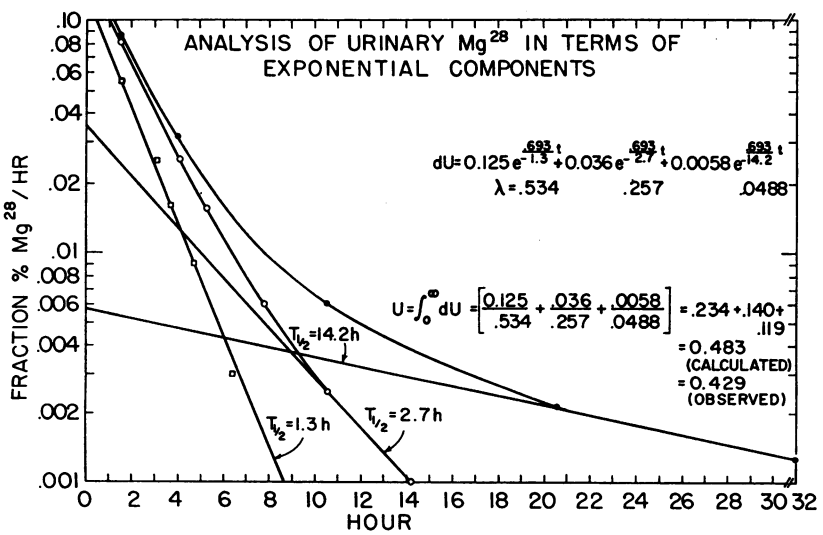

FIG. 4. ANALYSIS OF URINARY Mg^{28} EXCRETION IN TERMS OF EXPONENTIAL COMPONENTS (13). λ = Fractional disappearance rates obtained from the expression $\lambda = 0.693/T\frac{1}{2}$; U = amount of Mg^{28} excreted in the urine; dU = differential of Mg^{28} excretion in the urine.

TABLE I

Pertinent clinical data on nine subjects given Mg^{28} intravenously

Patient	Diagnosis	Age	Sex	Wt.	Time for equilibration	Exchangeable Mg^{++}	
						Total	
		yrs		*kg*	*hrs*	*mEq*	*mEq/kg*
C	EHT*	46	♀	82.6	39	300	3.6
Bl	EHT	72	♀	61.7	40	220	3.6
K	EHT	52	♀	76.0	40	277	3.6
W	EHT	53	♀	64.2	48	232	3.6
H	RA	55	♂	73.1	49	365	5.0
S	EHT	64	♀	55.9	49	380	6.8
L	EHT	55	♀	83.5	61	304	3.6
Bi	EHT and LHD	62	♂	83.2	88	1,040	14.1
D	EHT	38	♀	46.4	89	431	9.3

* EHT = essential hypertension; RA = rheumatoid arthritis; LHD = luetic heart disease.

among the early data and the interpretation thereof, Mendel and Benedict showed quite clearly that the subcutaneous injection of various Mg^{++} salts was followed by rapid urinary excretion of the ion, whereas intestinal excretion, if present at all, was insignificant. Hirschfelder and Haury (19), however, reported that in seven normal adults 40 to 44 per cent of an ingested dose of Mg^{++} appeared in the urine within 24 hours. Tibbets and Aub (20) by means of classical balance techniques studied the excretion of Mg^{++} in normal subjects; they found that individuals on an intake of 0.6 to 0.9 g per day excreted 0.5 to 0.8 g, of which slightly over half was in the stools. Smith, Winkler and Schwartz (21) studied the excretion of Mg^{++} in dogs after intravenous administration of $MgSO_4$ and concluded that during the first three to four hours the Mg^{++} distributed itself throughout the extracellular fluid, while during subsequent hours there was evidence that some of the ion was being segregated from the extracellular fluid and not excreted. Both the isotopic studies by Rogers and Mahan on rats (22) and the current study on humans are in general agreement with this earlier nonisotopic work. Rogers and Mahan concluded that in rats magnesium was present in two or more physiologic states, one with a turnover time of 1.2 hours, and the other with about 25 hours. As noted earlier, our data suggest two rapidly equilibrating pools with half-times of 1 and 3 hours, a slower one of 14 to 35 hours, and one (or more) with a very slow turnover of the order of 2 per cent per day or less.

In the present work, intestinal absorption of Mg^{++} was low, but the data were derived from single experiments in two individuals. It is possible that lack of absorption was due to the formation of relatively insoluble Mg^{++} compounds in the alkaline medium of the intestine or that absorption is dependent upon body need. The fact that only about 1 per cent of an intravenous load of Mg^{28} appeared in the stools is strongly against the possibility that magnesium is absorbed from the gut at one point and re-excreted into it at another. The marked disparity between these data and some of those derived from nonisotopic studies (19) indicates the need for further study with the isotope, possibly using several other salts of Mg^{++}. However, Aikawa, Rhoades and Gordon (23) using $Mg^{28}Cl$ in man, and Aikawa (24) using $Mg^{28}SO_4$ in rabbits, also found low urinary excretion after oral administration of the isotope.

If approximately three-fourths of the total body Mg^{++} is assigned to bone (14, 15) and the assumption made that none of this is exchangeable, the present data indicate that perhaps half of the remaining Mg^{++} has exchanged with the isotope 40 hours after intravenous administration. It is more likely that some of the bone Mg is exchangeable (12). Although the exact size of this fraction may be in question, it is clear that somewhere there is a relatively large pool with a slow turnover rate and presumably this is made up largely by the magnesium in bone. Based on the analyses previously cited (14–16) only about 10 to 35 per cent of the total Mg^{++} stores can be assumed to have exchanged with the isotope after 40 to 90 hours of equilibration.

SUMMARY

Studies with Mg^{28} in man suggest that gastrointestinal absorption of Mg^{++} is very limited. Fol-

lowing intravenous administration the isotope rapidly appears in the urine but only insignificant amounts appear in the stool. This indicates that most of the magnesium in the stools is of exogenous origin. Equilibration of the isotope with magnesium in the body is slow and at 40 to 60 hours it amounts to about 10 to 25 per cent of the total; at 90 hours perhaps a third of the body's magnesium has reached equilibrium with the isotope. Graphical analysis of urinary Mg^{28} curves in terms of exponential components yielded a slow component with a half-time of 14 to 35 hours accounting for 10 to 15 per cent of the injected dose, and two more rapid components with half-times of 1 and 3 hours each, accounting for 15 to 25 per cent of the injected dose. The large fraction remaining—from about 25 to 50 per cent of the body's total—has a turnover rate of less than 2 per cent per day. These turnover values must be interpreted with caution because of possible effects from the significant amounts of dietary magnesium in addition to the effect of that administered with the low specific activity Mg^{28}.

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