Mg^{28} kinetics in man[1]

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AVIOLI, LOUIS V., AND MONES BERMAN. *Mg^{28} kinetics in man.* J. Appl. Physiol. 21(6): 1688–1694. 1966.—Following the intravenous injection of Mg^{28} to 15 normal adults on metabolic balance regimens, a multicompartmental-type analysis was used to describe the isotopic and metabolic data. The compartmental sizes and transfer constants were obtained with the NIH-OMR-SAAM program and an IBM 7094 computer. Only 15% of the estimated whole-body magnesium could be accounted for by rapid exchange processes with total body exchangeable magnesium averaging 3.54 mEq/kg body weight. Two rapidly exchanging compartments when combined approximated extracellular fluid in distribution and a third, containing over 80% of the total exchangeable pool, reflected intracellular magnesium. The data also suggest the presence of another magnesium compartment accounting for most of whole-body magnesium which exchanges very slowly with an estimated biological half-life of 1,000 hr.

mineral metabolism; compartmental model for magnesium; computer analysis of tracer kinetic data; magnesium balance in normal man

THERE IS remarkably little information presently available regarding factors regulating magnesium metabolism in man despite the well-known contribution of magnesium to enzyme activity and its abundance in calcified tissue. Despite the importance and ubiquitous role of magnesium in metabolic processes, scanty information is currently available with respect to the incidence and significance of clinical deviation resulting from deficits and excess of this cation. This is due primarily to *1*) the absence of satisfactory quantitative methods for the determination of magnesium levels in serum and tissue, *2*) the lack of sufficiently large normal population studies, and *3*) the use of low specific activity Mg^{28} preparations which, when combined with the short (21.8 hr) physical half-life of Mg^{28}, precludes adequate evaluation of in vivo magnesium dynamics.

In the present study a series of normal subjects have been subjected to combined metabolic balance-isotopic Mg^{28} turnover studies in order to define an interval model for magnesium metabolism in man. The data thus derived were subjected to compartmental analysis using digital computer techniques.

MATERIALS AND METHODS

Fifteen normal volunteers ranging in age from 23 to 34 years were studied under metabolic balance conditions in the Clinical Research Center ward. For 14–21 days before the administration of the isotope and during the subsequent period of isotopic analysis the patients were on constant weighed diets containing 500 mg of calcium (Ca), 850 mg of phosphorus (P), 14.7–27.5 mEq of magnesium (Mg), and less than 10 mg of hydroxyproline in the form of protein. Admission weight was maintained throughout hospitalization. Water intake was unrestricted, although measured, during the course of the study. All patients were kept ambulatory and physically active. On the day of isotope administration, 150–175 μc of $Mg^{28}Cl$ (specific activity of Mg^{28} greater than 10.66 μc/mg) (Iso Serve, Cambridge, Mass.) were rapidly injected into an antecubital vein from a calibrated syringe prior to the morning meal. Thereafter, blood samples were obtained by venipunctures from the opposite arm at 15, 30, and 45 min and at 1, 2, 4, 8, 12, 16, and 24 hr. For the remainder of the study plasma was obtained at 12- to 24-hr intervals for periods ranging from 2 to 6 days.

During the first day urine was collected at hourly intervals for the first 4 hr and at 4-hr intervals for the subsequent 20 hr. Thereafter urine was collected during 8- or 12-hr periods for the remainder of the study. Urine collections were acidified with 5–10 ml concentrated hydrochloric acid and preserved by refrigeration. Feces were collected for 2- to 6-day periods, homogenized to 1,500 ml, and aliquots were obtained for stable and radioactive Mg analysis. All fecal collections were initiated and terminated with enemata to ensure complete recovery.

Diets, sera, and excreta were analyzed for magnesium,

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with chemical determinations performed in duplicate on two different aliquots of each specimen. Stable magnesium concentrations in whole serum, serum ultrafiltrates, urine, feces, and diets were determined by flame spectrophotometry according to the methods of Alcock, MacIntyre, and Radde (5).

The Mg^{28} content of blood, urine, and feces was measured directly in a well-type scintillation counter utilizing pulse height spectrometric analysis and a 3-inch thallium-activated NaI crystal. Discriminator settings were selected to give optimum statistical accuracy with a counting error no greater than 1 %. Mg^{28} determinations were made on 4 ml of plasma, on 200-ml aliquots of homogenized fecal specimens, and on 20-ml aliquots of urine. Aliquots of the injected $Mg^{28}Cl$ solution also were counted daily and the radioactivity of serum and excreta expressed either as percent of injected Mg^{28} or percent of injected Mg^{28} per 4 ml of serum.[3]

Ultrafiltrates were obtained from the serum by anaerobic techniques utilizing an Araflo ultrafiltrate apparatus (Applied Research Associates, New York City) with nitrogen filtration pressures approximating 300 lb. More than 4 ml of ultrafiltrate were obtained from 10 ml of serum in 5–6 hr.

Twenty-five microcuries of Mg^{28} also were administered orally to 8 of the 15 normal subjects following an overnight fast and cumulative stool Mg^{28} was measured until the radioactivity was no longer detectable. Since fecal magnesium appears to be primarily magnesium from food which is not absorbed by the body, rather than magnesium secreted by the intestine (3, 14, 21), the cumulative fecal Mg^{28} excretion was considered a reliable index of magnesium absorption.

In order to estimate the absolute amount of magnesium absorbed per day by the intestine, one must assume the same probability of absorption for the endogenously secreted magnesium as for the dietary magnesium. Under metabolic balance conditions the following relation holds:

$$\% A_{Mg} = \left[1 - \left(\frac{F_{Mg} - E_{Mg}}{D_{Mg}}\right)\right] \times 100 \qquad (1)$$

where F_{Mg} represent total fecal magnesium (mEq/d); E_{Mg}, endogenous fecal magnesium (mEq/d); A_{Mg}, absorbed magnesium (mEq/d); and D_{Mg}, dietary magnesium (mEq/d). The magnesium content of diets and feces was measured directly whereas the endogenous magnesium was calculated from the amount of fecal Mg^{28} accumulated during the intravenous Mg^{28} studies. When radioactive magnesium is administered intravenously all the fecal radioactivity is endogenous. Assuming the specific activity of the magnesium excreted into the gastrointestinal tract at a given instant to be identical to that of urine magnesium at that moment, the quantity of endogenous fecal magnesium may be determined by the following relationship:

$$E_{Mg} = U_{Mg} \times \frac{f^s}{f^u} \qquad (2)$$

where U_{Mg} = urinary stable magnesium excretion rate (mEq/d), f^s = the fraction of intravenously administered Mg^{28} in the feces, and f^u = the fraction of intravenously administered Mg^{28} collected in urine. Since the studies were terminated at 2–6 days, values for f^u and f^s were selected for equal time intervals with a correction for the fecal excretion assuming an intestinal transit time of one day.

RESULTS

Renal and fecal excretion of Mg^{28}. Following the intravenous administration of Mg^{28}, 7.27–17.3 % (mean = 10.6) was normally recovered in the urine within 48 hr in six subjects, 7.17–17.1 % (mean = 11.6) within 72 hr in four subjects, and 15.0–23.4 % (mean = 16.9) within 6 days in five subjects. These values are significantly lower than those reported by Silver, Robertson, and Dahl (21) and Aikawa and associates (3) wherein 35–40 % of injected Mg^{28} was recovered in the urine 3–4 days after intravenous administration. The apparent discrepancies probably result from the larger magnesium intake of their patients and radioactive magnesium doses of much lower specific activity. Cumulative fecal radioactivity averaged 1.78 % at 48 hr (range, 0.95–4.3), 1.22 % at 72 hr (range, 0.28–2.31), and 2.61 % at 6 days (range, 0.86–3.53). These values are in agreement with the reported observations of others (3, 14, 21). Calculated endogenous magnesium secretion in all 15 patients ranged from 0.55 to 2.76 mEq/day with mean values for 48 hr, 72 hr, and 6 days of 1.11, 0.70, and 1.64 mEq/day respectively. On diets ranging from 14.7 to 27.5 mEq/day, calculated magnesium absorption (*equations 1* and *2*) of the 15 subjects averaged 44.8 % (range, 37.2–54.3). These findings

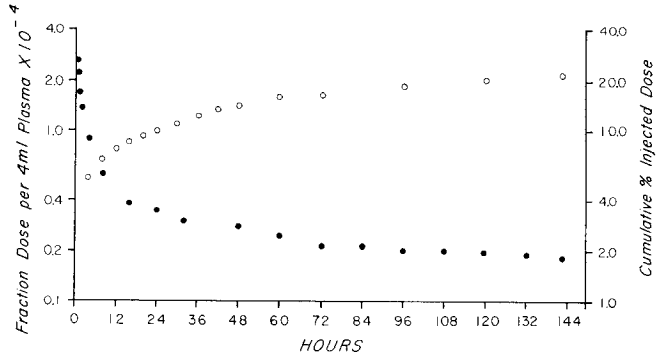

FIG. 1. Plasma disappearance and cumulative urine Mg^{28} in *patient WL.* Serial plasma Mg^{28} values are represented by the closed circles; cumulative urine Mg^{28} values are represented by the open circles. The right and left ordinates refer to urine and plasma concentrations, respectively. Plasma data may be fitted to a sum of three exponentials: β (t) = $7.45e^{-0.618t} + 1.64e^{-0.0897t} + 0.315e^{-0.0037t}$.

[3] Plasma Mg^{28} values were expressed in terms of "4 ml of serum" in order to facilitate digital computer analyses of the plasma and urinary stable and radioactive magnesium data simultaneously.

confirm those of other investigators wherein 44.3 % of orally administered Mg^{28} was absorbed by patients on intakes approximating 20 mEq of magnesium per day (14). Magnesium absorption of the eight subjects who received an oral dose of Mg^{28} was calculated by assuming:

absorbed Mg^{28} = 100 − % oral dose in cumulative fecal collection

In these subjects magnesium absorption ranged from 37.8 to 55.9 % (mean = 45.7) confirming the values obtained utilizing *equations 1* and *2*.

Total and ultrafilterable Mg. The mean concentrations of total and ultrafilterable magnesium for the 15 subjects were 1.92 and 1.35 mEq/liter, respectively. When expressed as a percentage of the total, 70.3 % of serum magnesium was ultrafilterable (range, 59.4–78.7 %).

Analysis. A typical set of data for serum and urinary Mg^{28} after a single intravenous injection is shown in Fig. 1. All the models proposed in this study were simulated on a digital computer, and the parameters were adjusted to the data by a least-squares fitting procedure. Acceptance of a model was based on the "goodness"[4] of the least-squares fit (7–9).

A compartmental model was proposed for the interpretation of the magnesium data. This choice was based on *1*) the fact that tracer kinetics in steady-state systems must be linear, and *2*) the observation that the tracer data obtained in these studies could be resolved readily into a sum of several exponentials (Fig. 1). The structure of the final model was evolved by starting with a "simplest" model consistent with theory, testing it against the data, and modifying it whenever inconsistencies occurred. In brief, the sequence of models proposed was as follows:

The plasma concentration of Mg^{28} fitted a sum of three exponentials, (Fig. 1). This requires a minimum of three compartments for the exchangeable magnesium. If one of the compartments is total magnesium in plasma, and if urinary Mg^{28} derives from plasma, then the integral of the plasma curve should be proportional to the cumulative urine curve. This was tested in several individual studies and proved not to be the case. It was necessary, therefore, to assume that plasma Mg^{28} consisted of at least two components not in rapid equilibrium with each other and that the data represented a combined sampling of both. Only one of these components served as a precursor for the urinary Mg.

Extrapolation of the cumulative urine and fecal data to infinite time in a number of studies indicated that not all of the injected label could be accounted for by these pathways. It was necessary, therefore, to introduce another "irreversible" path for the tracer magnesium and, consequently, the model shown in Fig. 2 was proposed. Other equally simple models could also have been proposed to fit the isotopic and balance data. This point will be raised again later.

In the model shown in Fig. 2, compartment 1 represents the pool of magnesium into which Mg^{28} was initially injected and the moiety that serves as a precursor to urine. This compartment interacts with two other compartments (2 and 3) forming together the exchangeable magnesium pool. Compartment five is the irreversible or slowly exchanging magnesium pool required to account for all the injected Mg^{28}.

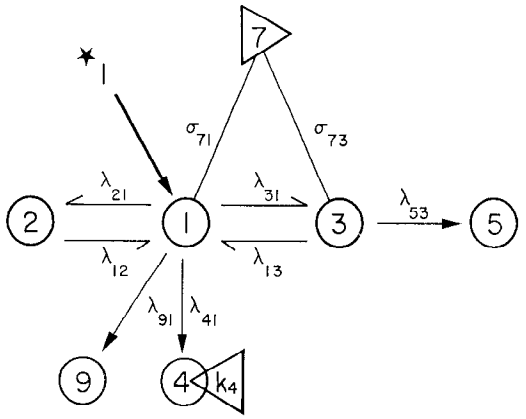

FIG. 2. Parallel 3-compartmental model used for initial analysis of Mg^{28} kinetic data. A central pool (compartment 1) is illustrated communicating directly with two other readily exchangeable magnesium pools (compartments 2 and 3). Compartments 4 and 9 represent irreversible urine and endogenous fecal loss, respectively; compartment 5 is defined as a slowly exchangeable magnesium pool. Triangle 7 is an operational unit and represents the sampling of a linear combination of material in compartments 1 and 3. The sigmas (σ_{71}, σ_{73}) are the coefficients in the linear combinations. The triangle touching a circle (K_4) identifies an operational unit representing a proportional sampling of a compartment. Lambdas (λ_{ij}) are fractional rate constants relating flows and pool sizes. The starred arrow identifies the site of Mg^{28} injection.

The triangles in the figure are called summers and are not part of the model; they represent data sampling. The triangle touching a circle represents the sampling of that compartment to within a proportionality constant. If the contents of any compartment i is f_i and the datum is q_i, the following relation holds:

$$q_i = K_i f_i \qquad (3)$$

where K_i is the proportionality constant.

Triangle 7 in Fig. 2 represents a sampling that is a linear combination of the contents of compartments 1 and 3, so that

$$q_7 = \sigma_{71} f_1 + \sigma_{73} f_3 \qquad (4)$$

σ_{71} and σ_{73} are the fractions sampled and are reciprocals of plasma equivalent spaces.

In testing the above model it was necessary to satisfy certain constraints. K_4 was set to unity, since the urine data were direct measures of the cumulative urine pool. σ_{71} is the reciprocal of the plasma equivalent space of distribution of pool 1 (V_1), and $\lambda_{41} V_1 C_1$ is the amount of stable Mg excreted in the urine per day, v_u, for a concentration C_1 of free magnesium in the plasma. It fol-

[4] No formal criterion is used in judging goodness of fit. Visual inspection of the plotted data and the calculated values is used to detect systematic deviations.

lows, therefore, that

$$\lambda_{41}V_1C_1 = \frac{\lambda_{41}C_1}{\sigma_{71}} = v_u \qquad (5)$$

Since v_u and C_1 were measured in each study the model was fitted subject to the constraint:

$$\sigma_{71} = \frac{C_1}{v_u}\lambda_{41} \qquad (6)$$

Analysis of all studies (both normals and abnormals) revealed that whereas a number of studies fitted very well, most did not. A systematic error appeared in the early part of the cumulative urine curve (0–14 hr): the predicted values were lower than the observed ones. Changes in the parameter values of the model could not eliminate this discrepancy.

It was then concluded that the experiments did not resolve a very rapid phase of Mg^{28} metabolism dominant almost immediately after injection, and that by the time the first observations are made (15 min) this phase is essentially over. During this initial phase a small amount of Mg^{28} appears in the urine. It was postulated, therefore, that for purposes of analysis a small fraction of the injected Mg^{28} was instantaneously diverted to urine and the model was adjusted operationally in such a way that the computer could calculate the fraction required in the urine instantaneously in order to fit the early urine data. (This rapid loss accounted for 0–1.9% of the injected Mg^{28} in the 15 normal subjects.) The model finally selected to represent the isotopic and balance data is illustrated in Fig. 3.

Summer (triangle) 8 represents the cumulative urine and is composed of a contribution (σ_{86}) from an artificial compartment 6 ($f_6 \equiv 1$) representing the instantaneous diversion to urine and a fraction, $\sigma_{,84}$ of cumulative urine. The constraint that $\sigma_{84} + \sigma_{86} = 1$ was imposed to normalize the total injected Mg^{28} to unity. Values and their uncertainties were obtained for all the parameters of the model subject to the constraints discussed above. Steady-state amounts (S) of stable magnesium for compartments 1, 2, and 3 and steady-state flows (Rho) between compartments were also computed. Compartment 5 is a slowly exchanging Mg pool and a return path (λ_{35}) should exist. The duration of the present experiments, however, were too short to permit the calculation of a λ_{35}. A dotted arrow, marked λ_{35}, is shown in Fig. 3 only to indicate the theoretical existence of such a path.

Figure 4 illustrates the experimental and calculated values for plasma and urine Mg^{28} in a typical normal subject (*WL*), according to the model depicted in Fig. 3. The range of values of the derived constants for the 15 subjects and the means for the population are given in Table 1. The calculation of steady-state compartment sizes was made with the assumption that compartment 5 was in steady state with the exchangeable magnesium pool, so that $Rho_{35} = Rho_{53}$. The mean total body ex-

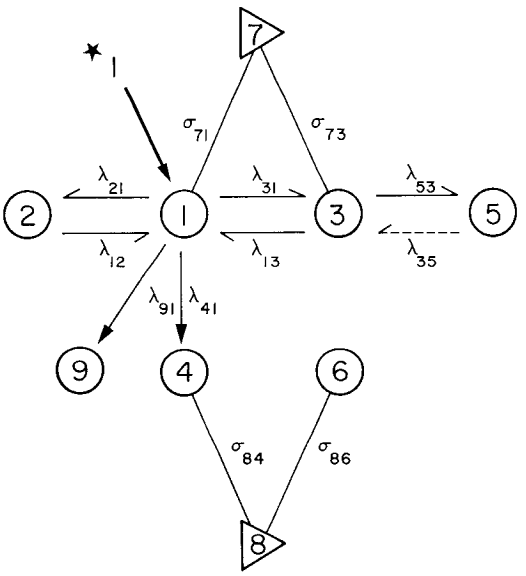

FIG. 3. Final compartmental model assumed for Mg^{28} kinetic analysis. Compartment 1 refers to ultrafilterable plasma Mg; compartments 2, 3, and 5 represent extravascular compartments. Compartment 5 is depicted as a slowly exchanging magnesium pool postulated to exist under steady-state conditions with slow turnover rate (λ_{35}). Compartment 6 is an operational unit introduced to account for the early appearance of small amounts of Mg^{28} in the urine. Compartments 4 and 9 refer to irreversible urine and fecal loss, respectively. The starred arrow identifies the site of Mg^{28} injection.

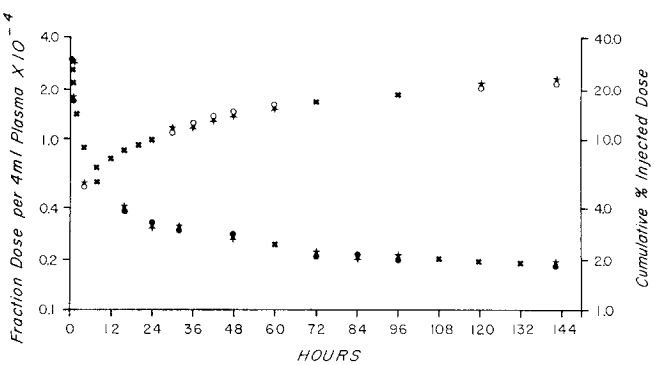

FIG. 4. Comparison of observed and theoretical plasma and urinary Mg^{28} concentration in *subject WL* as conditioned by the model illustrated in Fig. 3. The circles and stars refer to experimental and theoretical values, respectively; open circles represent cumulative urine and closed circles plasma values. The crosses represent instances wherein the difference between theoretical and experimental values were too small to be differentiated by the computer printout.

changeable magnesium of 3.54 mEq/kg body weight (Table 2) represents only 15% of the total body magnesium content of 30 mEq/kg body weight (1) and confirms other observations (3, 18, 21). The greatest part (87%) of the exchangeable magnesium pool is compartment 3. Compartments 1 and 2 averaged 0.217 and 0.231 mEq/kg, respectively. Neither compartments 1 nor 2 could be identified with known physiological entities since each represented a space larger than that assumed

TABLE 1. *Summary of calculated multicompartmental model parameters of 15 normal subjects*

	Range	Mean±SE
Fractional rate constants, fraction/hr		
λ_{12}	0.173–1.5	0.531±0.089
λ_{21}	0.214–0.868	0.396±0.044
λ_{13}	0.00881–0.0484	0.0301±0.0026
λ_{31}	0.192–0.512	0.325±0.021
λ_{53}	0.000193–0.0147	0.00556±0.00098
λ_{41}	0.0007–0.0340	0.0165±0.0022
λ_{91}	0.00091–0.00999	0.00297±0.00063
Intercompartmental flow constants, mEq/kg hr		
Rho_{41}	0.00189–0.00590	0.00407±0.00026
$Rho_{21,\ 12}$	0.0515–0.1530	0.0819±0.0067
$Rho_{31,\ 13}$	0.0451 0.0909	0.0675±0.0030
$Rho_{53,\ 35}$	0.–0.0396	0.0156±0.0025

Values refer to compartmental model illustrated in Fig. 3.

TABLE 2. *Summary of calculated compartment sizes and exchangeable magnesium of 15 normal subjects*

	mEq	mEq/kg	L, liters	% Body Wt
S_1				
Range	7.75–32.7	0.156–0.329	4.71–16.3	8.06–17.0
Mean ± SE	16.2±1.66	0.217±0.011	8.46±0.82	11.3±0.59
S_2				
Range	4.02–48.6	0.081–0.576	2.07–20.0	4.18–29.8
Mean ± SE	18.1±2.9	0.231±0.032	9.41±1.54	12.1±1.67
S_3				
Range	104–537	1.76–5.32	53.6–269	90–273
Mean ± SE	229±29	3.09±0.23	126±14.3	161±12
E				
Range	116–603	2.06–5.77		
Mean ± SE	263±32	3.54±0.24		

Values refer to compartmental model illustrated in Fig. 3. S_1, S_2, and S_3 refer to compartments 1, 2, and 3, respectively. E = total exchangeable magnesium. L = plasma equivalent space of distribution.

for total serum volume[5] and smaller than calculated extracellular fluid volume.[5] The sum of compartments 1 and 2 in each case corresponded closely to estimated extracellular fluid volume, with mean values for the normal subjects equal to 23.4% of body weight. As noted in Table 2 the calculated plasma equivalent space of compartment 3 (mean = 126 liters) exceeds total body water estimates. This observation probably reflects the high intracellular and osseous concentration of stable magnesium relative to plasma concentrations (2).

Despite prolonged 14- to 21-day adjustment periods none of the patients satisfied the rigid requirements of steady-state kinetics. Table 3 illustrates calculated magnesium balance in the 15 normal subjects. Positive and negative "balances" were noted, respectively, in 11 and 4 subjects.

DISCUSSION

It has been shown in man and other species that after the intravenous administration of Mg^{28} the decline in plasma or urinary specific activity can be expressed as the sum of several exponential terms (3, 4, 10, 11, 15, 16, 21). The method of graphic analysis of plasma or urinary specific activity measurements and the resolution of the disappearance curves into a series of exponential functions has been heretofore widely applied to studies of Mg^{28} kinetics. Most often the data have been treated with the assumption that each exponential function represented a discrete magnesium compartment with independent rates of turnover. On the basis of such analyses applied to urinary Mg^{28} specific activity curves, Silver et al. (21) defined three exchanging magnesium compartments in man with half-times of 35 hr, 3 hr, and 1 hr, respectively. MacIntyre and associates (17) also described three exchangeable magnesium compartments in man with "fast," "intermediate," and "slow" turnover containing 7.3, 24.4, and 98.7 mEq of magnesium, respectively. Zumoff (23) analyzing curves in normal subjects again described three components with half-lives of 15, 40, and 340 min. The errors intrinsic to analyzing plasma or urine specific activities via graphic analytical techniques as well as the inability to quantitate the net movement of material between individual exchangeable compartments using these techniques prompted the present multicompartmental analytic approach to magnesium metabolism. The compartment symbolizes a totality of particles within the system that are operationally indistinguishable from each other. This may or may not correspond to an identifiable physiological entity.

In the present model over 85% of the exchangeable magnesium pool was accounted for by compartment 3. Of total body magnesium of man, 60% can be accounted for by bone and 20% by muscle (1). The magnesium content of soft tissues in man approximate 400–420 mEq or 20% of total body magnesium (1). The rapid exchangeability of this soft tissue magnesium with injected Mg^{28} as compared to the much slower skeletal muscle and bone magnesium exchangeability has been documented repeatedly in animals and man by many investigators (4, 10, 11, 15, 17). One could argue, therefore, that the calculated whole-body exchangeable magnesium content in the present study representing 15% of the whole-body magnesium primarily reflects intracellular magnesium. Not only is it premature to identify specific compartments with physiological magnesium tissue pools at this stage of the analysis but one must consider that varied rates of exchange of individual tissues may be incorporated in the same compartment. Foremost is the likelihood that one is not sampling single compartments when one samples individual tissue. Despite evidence that bone and skeletal muscle have very slow rates of magnesium turnover there are observations attesting to varied rates of exchange within skeletal mus-

[5] These calculations assumed serum volume = 0.05 body weight and extracellular fluid volume = 0.20 body weight.

TABLE 3. *Calculated stable magnesium balance in normal subjects during Mg^{28} kinetic studies*

Subj	Absorbed Mg	Urinary Mg	Endogenous Fecal Mg	Mg Balance*	Observed* Rho_{35}	Calcd Adjusted Rho_{35}	Calcd Prestudy Absorbed Mg
WS	0.324	0.263	0.042	+0.019	0.5434	0.5244	0.313
CB	0.355	0.288	0.029	+0.038	1.844	1.806	0.348
EH	0.285	0.192	0.023	+0.070	2.081	1.961	0.275
ED	0.315	0.291	0.028	−0.004	0.3177	0.3217	0.318
RP	0.400	0.342	0.039	+0.019	1.638	1.619	0.395
RL	0.370	0.196	0.115	+0.059	1.921	1.862	0.359
JO	0.330	0.257	0.024	+0.049	1.478	1.429	0.319
RO	0.376	0.208	0.046	+0.122	1.364	1.242	0.343
WB	0.275	0.171	0.024	+0.080	0.0	0.0	
AG	0.341	0.304	0.023	+0.014	0.8265	0.8125	0.335
JD	0.581	0.550	0.100	−0.069	0.0994	0.1063	0.621
NO	0.400	0.283	0.067	+0.050	0.0	0.0	
DS	0.396	0.279	0.066	+0.051	2.178	2.127	0.387
WL	0.351	0.329	0.084	−0.062	0.4239	0.4859	0.402
HS	0.306	0.412	0.025	−0.131	0.9621	1.093	0.348

Values are in mEq/hr. Magnesium balance = absorbed Mg − (urinary Mg + endogenous fecal Mg). Calculated adjusted Rho_{35} = observed Rho_{35} − Mg balance. Calculated prestudy absorbed Mg = (adjusted Rho_{35}/observed Rho_{35}) × absorbed Mg. * As determined by constraints of comparmental model in Fig. 3.

cle and bone. Rogers and Mahan (19) noted at least two components in rat skeletal muscle, one exchanging rapidly (within 1.2 hr), but more than half exchanging very slowly, requiring at least 25 hr. Gilbert (13) studied the uptake of Mg^{28} in frog muscles and found three components lasting 0.5, 30, and 300 min and accounting, respectively, for 0.21, 0.71, and 0.67 mmoles of magnesium per kilogram of muscle. He also noted that about 75–80% of muscle magnesium was nonexchangeable and difficult to remove by diffusion.

There is still no general agreement as to the form in which magnesium occurs in bone despite the observations that bone cortex has the highest concentration of magnesium in the body (1). It appears that a large proportion (at least 70%) of the total bone magnesium is located on the surfaces of bone crystals either as Mg^{2+} or $MgOH^{+}$ ions adsorbed at the primary cation adsorbing centers or as Mg^{2+} ions replacing surface Ca^{2+} ions of the crystal lattice (22). The results of feeding magnesium-deficient diets in animals (12) and man (17) lend support to the observation that part of the bone magnesium is in a readily exchangeable labile form. In this regard MacIntyre and associates (17) have reported that there are two components to bone magnesium equilibration with Mg^{28} with relatively intermediate and slow rates of exchange when compared to extracellular magnesium.

The present study indicates that in man there are at least three exchangeable magnesium pools with varied rates of turnover reflected in a 6-day study. Compartments 1 and 2, exemplifying pools with a relatively fast turnover, together approximate extracellular fluid in distribution; compartment 3 an intracellular pool containing over 80% of the exchanging magnesium, with a turnover one-half that of the most rapid pool; and compartment 5, which probably accounts for most of whole-body magnesium. Since only 15% of whole-body magnesium is accounted for by relatively rapid exchange processes, approximately 25.5 mEq/kg of body magnesium (0.85 × 30 mEq/kg) is either nonexchangeable or exchanges very slowly.

Assuming *1*) a steady state wherein $Rho_{35} = Rho_{53}$ (Rho_{35} = 0.0156 mEq/kg hr, Table 1) and *2*) that the slowly exchanging body magnesium could be accounted for by a single compartment (compartment 5, Fig. 3), then:

$$\frac{Rho_{35}(\text{mEq/kg hr})}{\text{compartment 5 (mEq)}} = \frac{0.0156}{25.5} = 0.00062/\text{hr} \qquad (9)$$

This represents a biological half-life of about 1,000 hr and would require an isotopic kinetic study of about 50 days for experimental verification. The short physical half-life of Mg^{28} and radiation hazards imposed by millicurie doses of Mg^{28} presently prohibit in vivo experiments of this nature in man.

One of the general assumptions necessary for this and similar types of kinetic studies is that the subjects are in a steady metabolic state during the experimental period. Despite 14- to 21-day dietary and metabolic adjustment periods none of the patients satisfied the rigid requirements of steady-state kinetics since all were either in negative or positive magnesium balance (Table 3). These variations, on magnesium intakes ranging from 15–28 mEq/day, are in accord with the observations of Seelig (20). The subjects may not have been in a magnesium steady state during the Mg^{28} study since compartment 5 is so large (85% whole-body magnesium) and its estimated turnover of 0.0006/hr so small that it had not yet adjusted to the constant dietary intake selected arbitrarily for each patient. If the assumptions and computations intrinsic to the analysis are correct the prestudy-absorbed magnesium can be determined for each subject as indicated in Table 3.

A number of aspects of the problem have not been solved. These include a concise interpretation of the analytical multicompartmental model system in terms of the actual biological system and the physiological significance of all the operational units of the model parameters. The constant, σ_{73}, represents the reciprocal of the space of distribution of a compartment that contributes to the labeled plasma magnesium. In general σ_{73} values were small and not shown in the present results. No efforts were made to isolate this compartment. It could represent nondializable plasma magnesium, but this is only suggestive. Accordingly, an effort will be made in future experiments to measure the radioactive magnesium label in both free and complexed fractions of plasma magnesium. The initial rapid urinary Mg^{28} loss accounting for 0.–1.9% of the injected dose in the 15 normal subjects has been interpreted as an instantaneous diversion of plasma Mg^{28} to urine. These observations could represent an incomplete distribution of the injected

Mg^{28} within the various plasma compartments during the 15-min period immediately following injection. The resulting disproportionately high plasma Mg specific activities could account for the observed excessive Mg^{28} excretion in the urine during this time. The model developed for the interpretation of magnesium kinetics in the 15 normal subjects is still not unique or final since it is obvious that other models exist with equally good fits of observed data.

Obviously, a model is a mere intermediate in the evolution of a complete understanding of the true system and must always be modified as new information is gathered. At this stage of understanding of magnesium kinetics the proposed model is adequate to serve as a test for the compatibility of the observations with formalized concepts and as a base of reference for the design of future studies. Further understanding of the magnesium system can be achieved only through the study of changes in parameters as a result of known physiological or biochemical abnormalities or perturbations (6).

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