Magnesium Absorption: Mechanisms and the Influence of Vitamin D, Calcium and Phosphate[1]

LAURIE L. HARDWICK, MICHAEL R. JONES,[2] NACHMAN BRAUTBAR[3] AND DAVID B. N. LEE[4]

Division of Nephrology (111R), Veterans Administration Medical Center, Sepulveda, CA 91343

ABSTRACT Magnesium absorption has been studied in both humans and animals under diverse experimental conditions. As a result, the data often appear confusing and conflicting. In this review we attempt to summarize information concerning Mg absorption and, where possible, to reconcile apparently conflicting observations. Most studies suggest that Mg is absorbed predominately in the distal intestine. At usual Mg intakes, Mg absorption occurs primarily by intercellular diffusional and solvent drag mechanisms. There is evidence for a saturable component of Mg absorption in the small intestine and the descending colon that is important at low dietary Mg intakes. Pharmacological doses of vitamin D increase Mg absorption in both vitamin D–deficient and vitamin D–replete animals. A substantial amount of Mg absorption, however, occurs independent of vitamin D. In addition, vitamin D may reduce Mg retention through increases in urinary Mg excretion. Intestinal interactions between Mg and calcium or phosphate have been demonstrated in both humans and animals. The nature of these interactions cannot be readily explained by data currently available. J. Nutr. 121:13–23, 1991.

INDEXING KEY WORDS:

- *magnesium absorption*
- *vitamin D*
- *calcium*
- *phosphate*

Intestinal magnesium transport has been studied under a variety of conditions in the past 20 years. However, there is still uncertainty about the major intestinal sites(s) of Mg absorption, transport saturability, dependence on metabolic energy, interactions with calcium or phosphate (P_i), and the influence of vitamin D (1–5). In several studies the major site for Mg absorption was shown to be the colon (6–8), whereas others demonstrated that the greatest rate of Mg absorption occurs in the duodenum (9, 10). Intestinal Mg transport has been reported to occur by diffusion (1), solvent drag (11) and/or a saturable process that may (8, 12) or may not (13) require energy. These results have been based on tracer techniques (13–17), in vivo intestinal perfusion preparations (8, 11, 18) and in vitro gut preparations (9, 12) in humans and animals. Conflicting results between studies can be traced to differences in methodology between studies using the same technique and to problems inherent to the use of each of these techniques in studying intestinal Mg transport. Although Mg absorption has been discussed in several review articles in relation to Mg metabolism (1–5), there has been no systematic analysis of the literature with regard to the mechanism of Mg absorption and the methodology used to deduce these mechanisms. We shall therefore review what has been reported about intestinal Mg transport with an emphasis on the methodology used. We will also summarize the potential role of vitamin D in regulating Mg absorption and possible interactions between Mg and Ca or P_i absorption.

SITE OF MAGNESIUM ABSORPTION

Chutkow (6, 7) in 1964 reported that the major site of Mg absorption was the colon in both Mg-deficient and Mg-replete young rats. Mg absorption was based on either fecal recovery of ^{28}Mg after injection into various sites along the intestine or on the amount of ^{28}Mg recovered in carcass (without the gut) and urine following orogastric feeding of ^{28}Mg. Using both techniques, Chutkow demonstrated that up to 70% of Mg

[1]This work supported by the Center for Toxicological and Chemical Exposure, Los Angeles, the National Kidney Foundation of Southern California and the Veterans Administration Medical Research Foundation.

[2]Present address: Baxter Health Care Corporation, Route 120 and Wilson Road, Round Lake, IL 60073-0490.

[3]Present address: 201 South Alvarado Street, Suite 402, Los Angeles, CA 90057.

[4]Please address correspondence to: David B. N. Lee, M.D., Department of Nephrology (111R), Sepulveda V.A. Medical Center, 16111 Plummer Street, Sepulveda, CA 91343.

0022-3166/91 $3.00 Received 1 August 1989. Accepted 15 June 1990.

absorption occurred in the colon. Specifically, he found that absorption of ^{28}Mg was not significantly lower when ^{28}Mg was injected into the cecum vs. when ^{28}Mg was injected into the stomach or the duodenum. Moreover, only 8% of total Mg absorption occurred in the first 75 cm of the small intestine when absorption was based on ^{28}Mg activity recovered in the carcass and urine.

Other investigators, however, have demonstrated significant absorption of Mg in the small intestine as well as the colon. Meneely et al. (8) using in vivo intestinal perfusion found that net transport rates of Mg in the colon were equal to or greater than those in either the jejunum or the ileum of weanling and adult rats. Behar (11) demonstrated net Mg absorption of similar magnitude from both the ileum and the colon of the rat in vivo. Ross (12) in rats found that Mg was transported more efficiently in the ileum than in the jejunum in the everted gut sac. Hendrix et al. (19) reported that both the rate of uptake and the total uptake of ^{28}Mg was greater in the jejunum, ileum and colon than in the duodenum of rats. Aldor and Moore (9) and Urban and Schedl (10) fond that the amount of Mg transported per unit weight decreased progressively through the gut in the rat. Based upon segment length or weight, therefore, their data indicate that Mg absorption predominates in the distal segments of the intestine.

In humans, peak plasma levels of ^{28}Mg have been consistently observed 4 to 7 h following oral administration (14–16). Graham et al. (16) documented that absorption began within 1 h of administration and that 80% of total absorption occurred within the first 6 h. From these data it has been inferred that Mg absorption in humans occurs uniformly throughout the small intestine with little or no absorption in the colon.

Marcus and Lengemann (20), however, found that as early as 2 h postintubation the majority of yttrium-91 given with a solid meal is already in the distal small intestine of rats. Moreover, by 4 h the entire dose was in the cecum and colon. These data suggest that the early plasma appearance of ^{28}Mg observed in human studies may be due to absorption of Mg from the distal rather than the proximal intestine as was previously thought.

Thus, most of the studies in humans and animals suggest that a significant proportion, if not the bulk of Mg, is absorbed in the distal intestine, that is, the ileum and colon. It is noteworthy that this conclusion is derived from studies based on different experimental methods, diet and age, or Mg status of the experimental subjects.

MECHANISM OF MAGNESIUM ABSORPTION

Theoretically, Mg can cross the intestinal epithelium by three mechanisms: passive diffusion, solvent drag and active transport. The major driving force for passive diffusion is the chemical gradient across the epithelium. Absorption by this process is expected to vary with the luminal Mg concentration and, in general, would not be expected to demonstrate saturation kinetics. Several studies have shown parallel increases in Mg absorption with increases in luminal Mg concentrations (2, 11, 12, 17), consistent with transport by a diffusional process. More detailed studies have confirmed that the concentration of ionic Mg on the luminal side of the absorption site is the major factor in the regulation of the amount of Mg absorbed over a given time interval (13, 16).

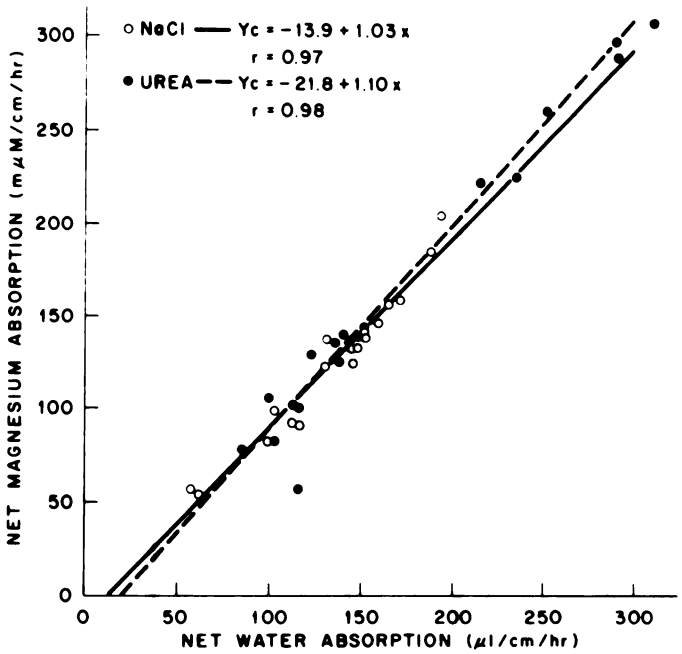

FIGURE 1 Relation between net Mg and water absorption from isotonic solutions of NaCl (- - -) or urea (—). Intestinal loops of terminal ileum were prepared from fasted rats weighing 150 to 200 g. Each rat was perfused with the test solution for 30 min. ^{28}Mg was added to the test solutions immediately before the experiment. Each point represents a single rat. Reproduced by permission from ref. 21.

Movement of water across the intestinal epithelium has the ability to transport solutes in the same direction. Solute transport by this process is thus accomplished through solvent drag. Using in vivo perfusion in rats, Behar (11, 21) observed a positive correlation between net water absorption and net Mg absorption (**Fig. 1**). In addition, factors that increased Mg absorption also generated increased water absorption.

Although Behar (11, 21) concluded that Mg absorption occurs primarily by a "solvent drag" mechanism, his study does not exclude the presence of other mechanisms of Mg absorption in the intestine. Behar (11) convincingly demonstrated that at a given Mg concentration, enhancing water flow enhances uptake of Mg. His study, by design, however, did not evaluate the relation of luminal Mg concentration to Mg uptake

because the effect of varying water flow on Mg absorption was investigated at only one Mg concentration. Ross and Brannan et al. (12, 18), in fact, have independently documented Mg absorption in rats and humans respectively, while keeping net water movement at zero throughout the study, indicating that other mechanisms are involved.

There has been considerable debate over whether intestinal Mg transport has an active component and over the relative importance of that component to total Mg absorption in the intestine. Animal studies based on in situ loop preparations, in vivo intestinal perfusion and in vitro gut sacs have consistently demonstrated that Mg absorption has a saturable component. Ross (12) documented a biphasic, nonlinear relationship between Mg absorption and luminal Mg concentration in rats when the Mg concentration was varied from 0.1 to 12 mmol/L in the small intestine (**Fig. 2**). Uptake increased rapidly until luminal Mg reached 2 mmol/L, at which point uptake began to plateau. Based upon Ross's data, Wilkinson (4) calculated a K_m of 0.35 mmol/L for the saturable component.

Meneely et al. (8), using in vivo intestinal perfusion, documented saturable transport of Mg in the colon of weanling and adolescent rats when the Mg concentration was varied from 0 to 5 mmol/L (**Fig. 3**). This saturable component was not present in suckling rats but rather developed and became more pronounced as the rat aged. The V_{max} and K_m were, respectively, 4.2 μmol/h and 0.9 mmol/L in the weanling rat and 2.7 μmol/h and 1.2 mmol/L in the adolescent rat.

Studies in humans also suggest that Mg absorption has a saturable component. Brannan et al. (18) studied Mg absorption in normal human jejunum and ileum by in vivo intestinal perfusion, using test solutions containing from 0 to 20 mmol/L $MgCl_2$. The rate of absorption in the jejunum rose progressively with a tendency toward saturation above 5 mmol/L (**Fig. 4**). The absorption characteristics in the ileum were similar to those in the jejunum, with the exception that no concentration-dependent absorption was noted in the ileum at Mg concentrations above 10 mmol/L.

Roth and Werner (13) employed a double dose technique using ^{28}Mg to determine fractional absorption of Mg in 23 fasting adults (**Fig. 5**). The amount of Mg absorbed was compared to the amount of Mg given in an oral dose. The amount of Mg absorbed varied with the amount of Mg fed in a cuvvilinear fashion. The data can be resolved into a component that is proportional to the amount of Mg ingested (nonsaturable) and another component that "saturates" as the amount of Mg ingested increases. Eleven percent of an oral dose was found to be absorbed by a linear process. The contribution by this nonsaturable component to total absorption, however, increased as the amount of Mg in the dose increased. Thus, according to Roth and Werner's data (Fig. 5), in fasting adults single doses of Mg up to 10 mmol (240 mg) would be absorbed predominately by the saturable mechanism. Whether similar kinetics would be observed in subjects ingesting Mg incorporated into a normal diet remains to be determined.

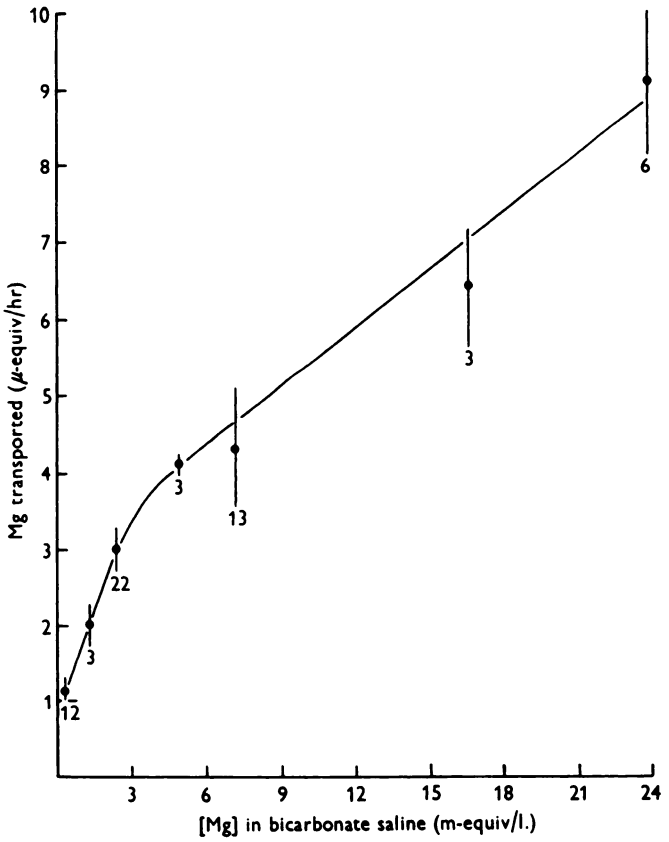

FIGURE 2 Relation between Mg transported per hour and circulating Mg concentration in rats. Bicarbonate-buffered saline was circulated through small intestinal segments, and fluid transported to the serosal surface was collected. Values are means ± SEM; the number below the error bars shows number of experiments in the group. Reproduced by permission from ref. 12.

It is important to point out that the plasma ^{28}Mg level is determined not only by the ^{28}Mg absorbed but also by a number of other factors, including urinary excretion of ^{28}Mg and the rate and the extent of ^{28}Mg redistribution into the extravascular and tissue compartments. For this reason, an intravenous dose of ^{28}Mg was also given and its decay was measured as an index for urinary excretion and redistribution of ^{28}Mg. The assumption is that once absorbed, the oral dose of ^{28}Mg is handled like the intravenous dose of ^{28}Mg. There have been no data in the literature to validate or repudiate this assumption. It does appear in general, however, that once in the circulation, ^{28}Mg is not affected by differences in Mg status. Dimich and Wallach (22) found a similar disappearance rate of ^{28}Mg from the mean plasma levels of intravenous doses of ^{28}Mg in patients with moderate hypomagnesemia secondary to alcoholism or malabsorption compared to controls. Individual variation was noted in kinetic parameters but did not appear to corre-

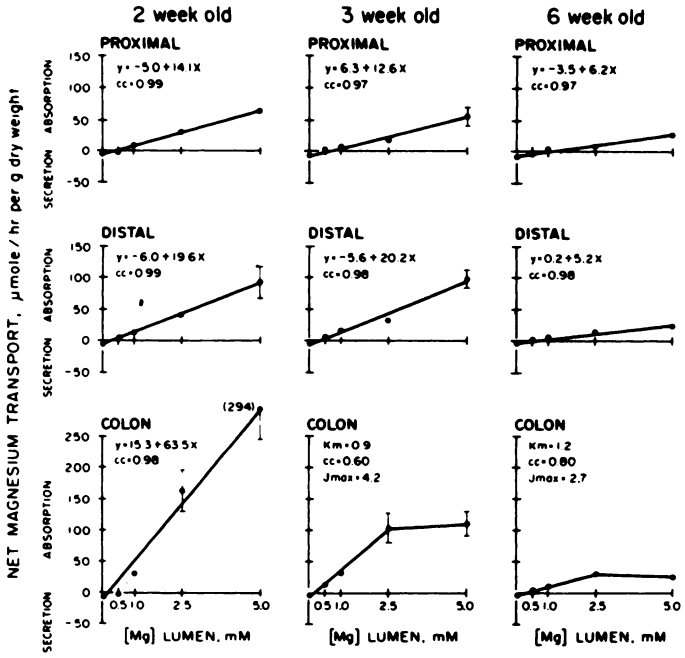

FIGURE 3 The relationship between rate of absorption of Mg and the initial [Mg] in the solution perfusing segments of the proximal and distal small intestine and the colon of rats. Values are means ± SEM, n = 29–30. In most cases, the SEM was small and could not be shown on the graph. In the proximal and distal small intestinal segments of all age periods, the relationship between net transport rate and luminal [Mg] was linear and evident by a straight line fit using the formula Y = A + (B+X) of the least square fit curves. In the colon segments of the suckling rats the relationship between net transport rate of Mg and luminal [Mg] was also linear; however, a curvilinear relationship was noted in the weanling and adolescent rats. The transport data for the colon fit Michaelis-Menten kinetics, with a K_m of 0.9 and 1.2 mmol/L for the weanling and adolescent rat's colon, respectively. Reproduced by permission from ref. 8.

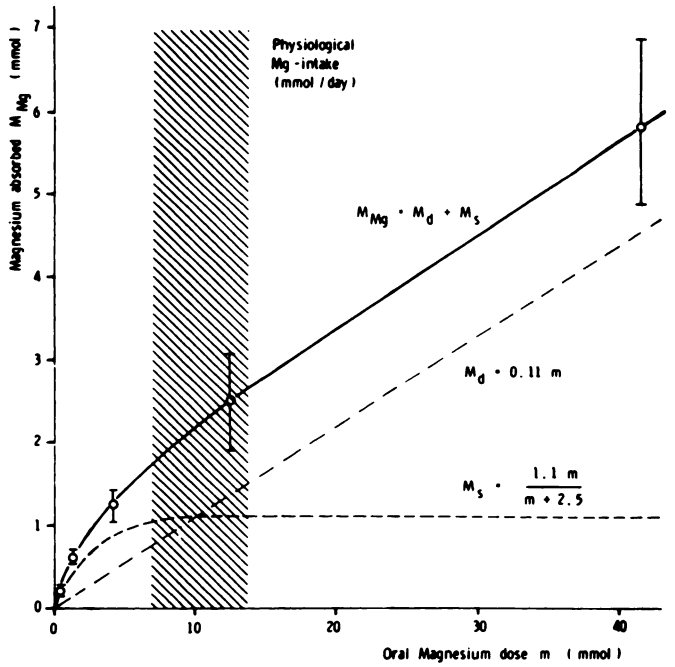

FIGURE 5 Relationship between Mg absorbed and oral Mg dose (mean ± 1 SD). Separation into a linear (M_d) and a saturable (M_s) component. Twenty-three people fasted overnight and were fed orally 2–4 µCi ^{28}Mg in 100 mL deionized water with varying amounts of stable Mg added. Five days later ^{28}Mg activity was measured by whole-body counter to determine fractional intestinal absorption. A tracer dose of ^{28}Mg was also given intravenously and counted by whole-body counter 5 d later to correct for excretion of absorbed ^{28}Mg activity. Reproduced by permission from ref. 13.

late with the underlying hypomagnesemia. This suggests that despite disturbances in Mg metabolism, the exchangability of injected ^{28}Mg is normal in the presence of hypomagnesemia and presumably Mg deficiency.

In sheep rumen, the major site of net Mg absorption, an active, saturable component of Mg absorption has also been reported (23–29). Martens and colleagues (24–26) reported that the mechanism of net Mg transport was saturable in the rumen when the Mg concentration of the bathing solution was elevated from 1.25 to 5 mmol/L. This saturable process has an apparent K_m of 2.43 mmol/L and was inhibited by either ouabain, dinitrophenol or cooling, suggesting that it was an active process. Furthermore, Scott (28) found no correlation between Mg absorption and luminal Mg concentration in jejunal or ileal loops from sheep. His data indicate that no more than a small fraction of Mg absorption occurs by simple diffusion in the small intestine.

In contrast to most of the studies discussed above, evidence for active Mg transport is lacking when studies have been conducted using the classical model for dem-

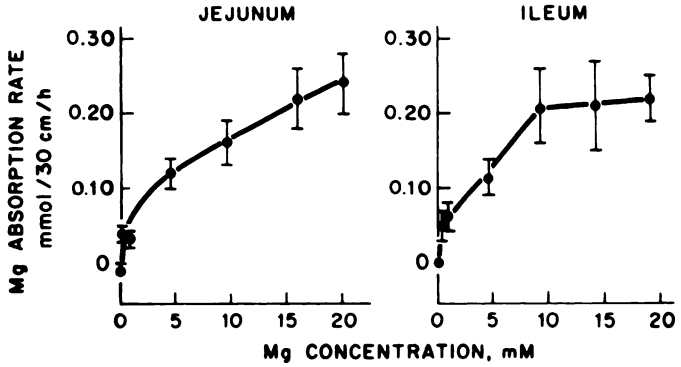

FIGURE 4 Mg absorption at different luminal Mg concentrations in human jejunum and ileum. Subjects consisted of healthy men and women with a mean age of 29 (range 21–42 y). Subjects were fasted 8 h prior to intestinal perfusion. Test solution contained 0.5% polyethylene glycol, 50 mmol/L NaCl, 5 mmol/L KCl and 10 mmol/L xylose. Values are means ± SEM, n = 5–11. Reproduced by permission from ref. 18.

onstrating transepithelial active solute transport, namely, the everted gut-sac preparation (30). Five studies have been published, using either the rat (9, 12, 19, 31) or rabbit (32) intestine. In the three studies conducted in rats, only Ross (12) initially placed ^{28}Mg and unlabeled Mg in both the serosal and mucosal fluid. Aldor and Moore (9) and Hendrix et al. (19) did not place Mg inside (serosal) the sac. Their experiments, therefore, were designed to measure Mg uptake into the serosal compartment in the presence of a transepithelial Mg concentration gradient rather than to demonstrate the intestine's ability to generate a transepithelial Mg concentration gradient, the hallmark of an active absorptive process.

In the one study in which Mg was placed in both the serosal and mucosal media (12), Mg did not concentrate against a gradient in either the jejunal or ileal segments of the intestine. This study, therefore, does not rule out active transport of Mg in other segments of the intestine such as the duodenum or the colon. In addition, some investigators have questioned the validity of this technique. Two studies in particular have shown that extensive damage occurs to the epithelium within 15 min of incubation in buffer and that this damage was progressive with time (33, 34). This effect was seen whether the sacs were perfused with 100% O_2 or a mixture of 95% CO_2.

Reddy (35) reported relatively high Mg^{2+}-ATPase activity present in the brush border throughout the small intestine of rats. He also observed a significant increase in the Mg^{2+}-ATPase activity in the jejunum and ileum of germ-free animals associated with an increase in Mg absorption as compared to conventional rats. Whether this Mg^{2+}-ATPase is directly involved in Mg absorption remains unknown.

Recently, Karbach (36) demonstrated active transport of Mg in the descending colon of the rat using the Ussing chamber. This system allows the measurement of steady-state solute fluxes in the absence of transepithelial electrochemical gradients. Under such conditions, Karbach observed a net transport of Mg in the absorptive or mucosal-to-serosal direction. This mucosal-to-serosal-flux consisted of a voltage-independent and a voltage-dependent component. The voltage-independent or cellular-mediated component was responsible for 37% of the flux and exhibited a V_{max} of 76.4 ± 34.9 nmol·cm^{-2}·hr^{-1} and a K_m of 0.52 ± 0.44 mmol/L (n = 6–12). Mg flux from the serosa to mucosa, however, was totally voltage-dependent and most likely occurred through the paracellular pathway.

Thus, available evidence suggests that passive diffusion, solvent drag and active transport all participate in intestinal Mg absorption. In the small intestine, evidence for active transport is mainly derived indirectly by the observation that the rate of Mg absorption does not remain constant (or linear) with increasing luminal Mg concentrations but is reduced at high luminal Mg concentrations. Such observations suggest, but do not establish, the existence of a cellularly mediated, saturable transport mechanism for Mg in the small intestine. For example, it is possible that high Mg concentrations may reduce the tight-junctional permeability, which in turn can lead to a reduction in the rate of diffusional Mg absorption, giving rise to the appearance of the participation of a saturable mechanism. Furthermore, the active absorptive mechanism that exists in the descending colon is probably important only under conditions of unusually low dietary Mg intake or rapid growth. Under the conditions of usual Mg intake, the active mechanism would be expected to be saturated and the bulk of Mg absorption would most likely be mediated through the diffusional and solvent drag mechanisms.

MAGNESIUM ABSORPTION AND VITAMIN D

Although vitamin D is an important regulator of Ca transport in the intestine, the importance of vitamin D for Mg absorption remains unknown (36–45). In several studies in vitamin D–replete rats, large doses of cholecalciferol and 1,25-dihydroxycholecalciferol increased absorption of Mg (38, 39). A similar effect on Mg absorption was not observed at lower doses of 1,25-dihydroxycholecalciferol in the colon of vitamin D-replete rats (36). In addition, studies have indicated that cholecalciferol increases Mg absorption in vitamin D–depleted animals. Levine et al. (37) observed augmentation of intestinal absorption of Mg in vitamin D–deficient rats given physiological levels of various vitamin D sterols (**Fig. 6**). In particular, Mg absorption was very sensitive to 1,25-dihydroxycholecalciferol with a maximum effect observed with only 20 pmol/d after 9 d. Interestingly, they also observed that increasing dietary Mg from 0.03 to 0.2% depressed percent net absorption of Mg in vitamin D–deficient rats after 3 d (37). Why Mg absorption was depressed by increases in dietary Mg in these vitamin D–deficient rats is unclear. However, these studies do suggest that there may be at least two intestinal transport systems for Mg: one that is vitamin D–dependent and another that is independent of vitamin D and exhibits adaptation to dietary Mg.

In vitamin D– and Mg-replete animals, pharmacologic doses of vitamin D markedly influence Mg absorption. Karbach and Ewe (45), using in vivo intestinal perfusion, documented that 100 ng/d of 1,25-dihydroxycholecalciferol given subcutaneously for 4 d markedly stimulated net Mg absorption in the colon of rats. This effect was independent of net water, Na or Cl movement. However, when lower doses of 1,25-dihydroxycholecalciferol were given to rats and Mg fluxes were studied under voltage-clamp conditions, 1,25-dihydroxycholecalciferol had no effect on Mg transport (36).

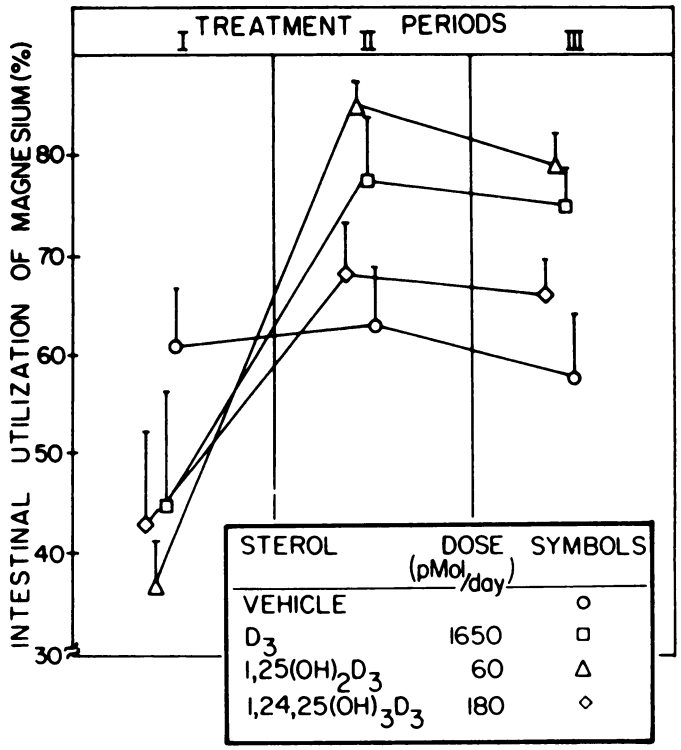

FIGURE 6 Intestinal utilization of Mg or net Mg absorption, expressed as percent of dietary intake, in rats fed a 0.03% Mg diet and treated for 9 d with vehicle, cholecalciferol, 1,25-dihydroxycholecalciferol, or 1,24,25-trihydroxycholecalciferol. Rats receiving vitamin D sterols were pair-fed with vehicle-treated animals. Values are means ± SEM. Mg absorption was increased significantly by period II with 1,25-dihydroxycholecalciferol ($P < 0.05$) and during period III by cholecalciferol and 1,25-dihydroxycholecalciferol ($P < 0.05$). 1,24,25-Trihydroxycholecalciferol failed to augment intestinal Mg absorption significantly during treatment period. Reproduced by permission from ref. 37.

In humans, the results of experiments on the effect of vitamin D on Mg absorption have been conflicting. Krejs et al. (39) noted that jejunal, but not ileal, Mg absorption was enhanced by a week of pharmacologic oral doses of 1,25-dihydroxycholecalciferol. Anast (32) reported an increase in Mg absorption when large doses of calciferol were given to a patient with vitamin D–resistant rickets. Wilz et al. (42), in contrast, noted no correlation between Mg absorption and plasma 1,25-dihydroxycholecalciferol concentrations in humans. Moreover, significant quantities of Mg were absorbed in the absence of detectable plasma 1,25-dihydroxycholecalciferol.

Hodgkinson et al. (43) orally administered pharmacologic amounts of ergocalciferol, 25-hydroxyergocalciferol, or 1,25-dihydroxycholecalciferol for 1 to 6 mo to patients with various disorders of Ca or bone metabolism. These treatments all enhanced Mg absorption but also increased urinary Mg so that Mg balance was unaffected. Likewise, Brickman et al. (44) observed a similar decrease in fecal Mg and a rise in urinary Mg when large doses of cholecalciferol were given, resulting in no change in Mg balance. Other investigators, however, have reported that high doses of vitamin D greatly enhance urinary Mg and actually lead to a substantial decrease in Mg retention in both animals and humans (38, 46, 47). Richardson and Welt (48), however, reported that the hypomagnesemia associated with ergocalciferol administration occurred with no changes in urinary or fecal Mg excretions in Mg-deficient rats.

The available data, therefore, suggest that a significant amount of Mg absorption is vitamin D–independent because it persists under conditions of vitamin D deficiency. Repletion of vitamin D is, however, associated with increments in Mg absorption. In vitamin D–replete animals and humans, pharmacologic doses of vitamin D appear to increase Mg absorption whereas spontaneous fluctuations in circulating levels of 1,25-dihydroxycholecalciferol have little effect on Mg transport. The importance of vitamin D–stimulated Mg absorption on overall Mg homeostasis remains uncertain, particularly in light of the dramatic increases in urinary excretion of Mg that have been associated with vitamin D administration.

CALCIUM AND MAGNESIUM INTERACTIONS

In humans, several laboratories have reported that increasing Ca in the diet significantly depresses Mg absorption (49, 50). Normal et al. (50) fed healthy humans a low (300 mg/d) or a high (2000 mg/d) Ca diet for 4 wk and perfused jejunal and ileal segments in vivo with solutions that contained no Ca and 5 mmol/L $MgCl_2$. They found a significant decrease in Mg absorption in the ileum of subjects fed the high Ca diet. Spencer et al (51), however, fed diets containing 200–2000 mg Ca/d for 29 to 43 d and saw no significant effect on fecal Mg. Leichsenring et al. (52) also observed no correlation between fecal Ca and fecal Mg when Ca was increased from 300 to 1200 mg/d in the diet of healthy women.

Increasing Mg in the diet has been reported to significantly decrease fecal Ca in humans (47, 52, 53). Brannan et al. (18), however, found in an intestinal perfusion study that increasing the concentration of Mg in the lumen decreased Ca absorption in the jejunum. Direct intestinal perfusion with various concentrations of soluble Mg or Ca salts in an isolated segment, however, may not reflect what is actually occurring in vivo. Ammann et al. (54) found significant absorption of ^{45}Ca when the ^{45}Ca was injected directly into the colon of rats. After an oral dose of ^{45}Ca, however, net ^{45}Ca absorption in the colon was negligible. The data suggest that Ca arriving in the colon from the small intestine is unavailable for absorption because of binding of Ca to complexing agents found in the intestine, such as oxa-

late or fatty acids. It is possible that Mg also binds to these complexing agents. The question is therefore raised whether interactions between Ca and Mg that are observed in isolated segments actually reflect what is occurring in the intact animal.

Moreover, the differences in methodology between studies makes it difficult to compare many of the human studies and to conclude whether there is any interaction between Ca and Mg in the intestine. Different levels of Ca and Mg were given, often within the same study. In some studies healthy subjects were used; in others the participants had a variety of diseases. Age and previous Ca and Mg intakes, both known to significantly affect Ca and Mg absorption, also differed between studies.

Although there are conflicting results in studies with humans (18, 49, 51, 52), all but one study (53) in rats have demonstrated that net absorption of Mg in vivo is depressed by a high Ca intake (10, 21, 54–61). The mechanism by which Ca and Mg interact, however, has not been well-defined. Several possible mechanisms have been proposed. These include competition for a common carrier system (55), a Ca-induced change in membrane permeability to Mg (52), and modulation of a specific Mg carrier by Ca (2).

A number of studies in animals, using a variety of in vivo and in vitro techniques, have indicated that there is direct competition between Ca and Mg for intestinal transport (21, 27, 55, 62). Behar (21), using an in vitro technique, reported that increasing the Ca concentration from 2 to 4 mmol/L in the incubation medium significantly reduced Mg transport in rat ileum at all Mg concentrations studied (**Fig. 7, 8**).

Work by other investigators with rats, however, indicates that the interaction between Ca and Mg is not always predictable. In the everted gut sac, Hendrix et al. (19) found that Ca and Mg are taken up preferentially in different portions of the intestine and that their interaction varied throughout the intestine. Specifically, Ca inhibited Mg transport in the ileum but not the duodenum, whereas Mg inhibited Ca transport primarily in the duodenum. Aldor and Moore (9) concluded that Mg transport was depressed by increases in luminal Ca from 0 to 1 or 5 mmol/L in the colon, but not in the small intestine. O'Donnell and Smith (61) investigated the interaction of Ca and Mg by studying short-term uptake in rat duodenal mucosa. Mg significantly inhibited the time-dependent uptake of Ca, but Ca did not significantly reduce uptake of Mg. Petith and Schedl (56), however, found that Ca absorption from the cecum and colon was depressed in Mg-deficient rats as compared to controls, but Ca deficiency had no effect on Mg absorption.

More recently, Karbach and Ewe (45) reported that increasing the Ca concentration from 1.25 to 10 mmol/L in in vivo intestinal perfusate has no effect on Mg absorption in the colon of rats. Likewise, increasing the

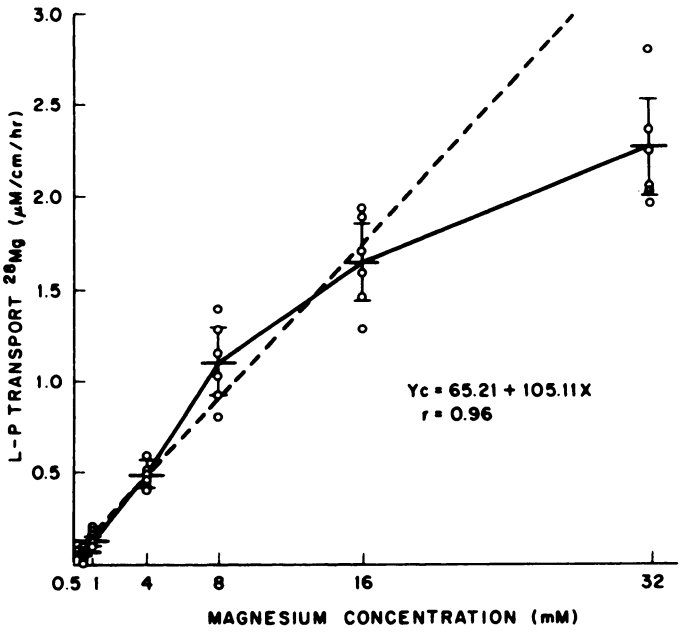

FIGURE 7 Effect of 2 mmol/L Ca on lumen to plasma (L-P) transport of Mg in ileum from 150–200 g rats. Relation between L-P transport and initial [Mg] from 0.5 to 16 mmol/L is shown as a broken line (r = 0.96). A trend line drawn by joining means of L-P transport at all [Mg] (0.5–32 mmol/L) is shown as a continuous line. Values are means ± SEM of six experiments. Reproduced by permission from ref. 21.

Mg concentration from 1.25 to 10 mmol/L had no effect on Ca absorption under similar conditions. When Karbach and Ewe examined Ca and Mg interactions further in the descending colon of the rat using the

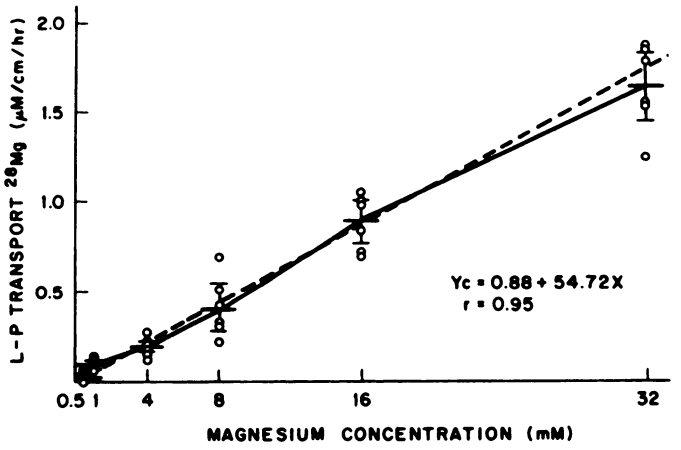

FIGURE 8 Effect of 4 mmol/L Ca on lumen to plasma (L-P) transport of Mg in ileum from 150–200 g rats. Relationship between L-P transport and initial [Mg] from 0.5 to 16 mmol/L is shown as a broken line (r = 0.95). A trend line drawn by joining means of L-P transport at all [Mg] (0.5–32 mmol/L) is shown as a continuous line. Values are means ± SEM of six experiments. Reproduced by permission from ref. 21.

Ussing system, however, they found that Mg had a significant effect on net Ca absorption. Specifically increasing the Mg concentration to 1.25 mmol/L decreased the mucosal-to-serosal flux of Ca by 50% and abolished net Ca absorption. The effect was due to a depression of the voltage-dependent component, that is, the paracellular pathway. Increasing the Ca concentration from 0.125 to 5 mmol/L had no effect on Mg transport. This study does not rule out that Ca at lower concentrations may significantly alter Mg absorption.

Much of the evidence for intestinal interactions between Ca and Mg has come from studies in which transport of one nutrient was studied in the absence of dietary intake of the other nutrient (21, 55, 56). This approach does not represent the situation of an animal consuming a normal diet. The deficient animals are often sick, and changes that alter cell permeability may occur. Indeed, Krawitt (57) found that whereas Mg-deficient animals absorbed more Ca than rats fed ad libitum, they absorbed the same amount of Ca as pair-fed controls. Another problem in interpreting these studies is that absorption of Ca and Mg was studied primarily in isolated segments rather than in the intact animal.

The results of the studies discussed previously do not exclude an adaptive effect of Ca upon Mg transport in the intestine. Ca may indirectly affect Mg absorption through changes in serum concentrations of Ca-regulating hormones. Alterations in serum Ca concentration are known to affect not only 1,25-dihydroxycholecalciferol but also parathyroid hormone (PTH). Although the effect of 1,25-dihydroxycholecalciferol on Mg absorption is not fully elucidated (see earlier discussion), PTH increases absorption of Mg in both humans and animals (1–5). The precise manner by which PTH affects Mg absorption, however, is uncertain. Although the involvement of 1,25-dihydroxycholecalciferol and PTH in mediating interactions between Ca and Mg in the intestine cannot be ruled out, these hormones are probably more important in the long-term adaptation to dietary Ca and Mg levels rather than in mediating short-term fluctuations. In addition, the in vitro evidence does suggest that there is interaction between Ca and Mg in the intestine independent of these hormones.

It has also been postulated that Ca may indirectly affect Mg absorption through changes in membrane permeability. Intestinal membrane permeability is sensitive to alterations in luminal Ca and Mg concentrations (63–65). Investigators have found that depletion of either luminal Mg or Ca increases tight junction permeability and thereby increases diffusion through the paracellular pathway (66, 67). While depletion of Ca and Mg in the lumen is an extreme state, one can postulate that physiologic changes in the concentration of Ca or Mg in the lumen might also influence diffusion through the paracellular pathway and may be important in the regulation of cation transport through this pathway. Further investigation will be required to test this hypothesis and to determine its importance in short- and long-term regulation of Ca and Mg transport.

PHOSPHATE AND MAGNESIUM INTERACTIONS

Increased P_i in the diet has been reported to depress Mg absorption, presumably by complexing with Mg to form an insoluble salt. O'Dell et al. (58) showed that increased dietary P_i, even more than Ca, increased the Mg requirement for maximal growth in both the guinea pig and the rat. Toothill (59) observed a significant decrease in Mg absorption when P_i was increased from 0.39 to 0.79% in 10-wk-old rats. This decrease was further reduced when both Ca and P_i were increased in the diet.

Other investigators, however, have not observed any effect of P_i on Mg absorption (49, 68). Clark and Rivera-Cordero (68) found in older rats that increasing P_i in the diet had no effect on Mg absorption and that there was no correlation between Mg absorption and P_i intake. Bunce et al. (69) reported that the effect of P_i on Mg absorption depended on the amount of Mg in the diet of weanling rats. High intakes of P_i (1.0%) lowered Mg absorption in the presence of high dietary Mg (0.1%), but P_i improved Mg absorption when Mg was limiting in the diet (0.01%). High Mg intakes, likewise, depressed P_i absorption to a greater extent the higher the P_i intake.

Clark (70) has also reported that the effect of Mg on P_i absorption in rats depends on P_i intake. Dietary Mg had no effect on fecal P_i at a P_i intake of 0.2%, significantly decreased it at an intake of 0.4%, and significantly increased it when the P_i intake was 0.8% and Ca intake was low (0.2%). Analysis of variance indicated that dietary Mg alone had no effect on fecal P_i, but rather it was the interaction between Ca and Mg that significantly altered P_i absorption.

In studies in humans, Heaton et al (71) showed that increasing dietary P_i decreased Mg absorption. Conversely, Briscoe and Ragan (72) observed a substantial decrease in P_i absorption when Mg was increased in the diet, although P_i balance did not appear to be significantly affected. Greger et al. (73) reported that subjects lost significantly more Mg in the feces when they consumed a high P_i diet (2443 mg/d) rather than a moderate P_i diet (843 mg/d). The apparent absorption of Mg dropped from 43 to 34% on the high P_i diet; however, urinary Mg also decreased on the high P_i diet, so that overall retention of Mg was unaffected by P_i intake. Both Spencer et al. (51) and Leichsenring et al. (52) observed no effect of P_i on Mg metabolism in men or women regardless of the Ca or Mg intake.

Studies on the interaction between P_i and Mg absorption are subject to the same concerns as the studies on Ca and Mg interaction. However, the data do suggest

that the interaction between P_i and Mg in the intestine is complex and dependent on several variables, such as age, luminal contents, as well as the dietary intake of Mg and P_i.

FUTURE FOCUS FOR STUDIES OF MAGNESIUM TRANSPORT

Although many investigators have studied Mg transport in the intestine, numerous questions remain. One major hindrance to studying Mg transport in the intestine has been the short half-life, expense and limited availability of the Mg radioisotope (^{28}Mg, half-life = 21.3 h). Technological advances may in the near future allow us to overcome this limitation. Investigators have shown that the stable Mg isotope (^{26}Mg) may be used to measure net Mg absorption and bioavailability in humans and rats (74, 75). One major limitation of this technique is that the analytical methods used are not sensitive enough to measure urine and plasma ^{26}Mg. As more sensitive methods of detection are developed, this technique will provide us with increased information on in vivo Mg absorption. In addition, the recent availability of intracellular fluorescent probes (Molecular Probes, Eugene, OR) for Mg makes it possible to follow Mg within cells as well as across membranes. Although still expensive, these probes have the advantage of being nontoxic and continuously available.

Future studies of Mg transport in the intestine need to characterize further the saturable component documented by Ross (12). Experiments employing the Ussing technique will eventually need to be conducted at low Mg concentrations in all segments of the intestine to determine whether Mg is actually able to concentrate against an electrochemical gradient. Assuming that the saturable process for Mg is a transcellular event as it is for Ca, then entry across the brush border membrane, diffusion across the intestinal cell, and extrusion across the basolateral membrane all need to be characterized.

In addition, most studies investigating Mg transport conducted in humans and animals have been done under specified experimental conditions. Mg has usually been given in chemical form in the absence of other dietary components. In addition, isolated segments of the intestine have primarily been studied. While studies of this type allow us to determine regional characteristics of Mg transport, they fail to answer how Mg is absorbed in the whole animal in the presence of dietary components. Future work will need to focus on Mg absorption as a component of a normal diet.

The relative importance of the paracellular nonsaturable and the transcellular saturable components to total Mg transport requires additional investigation. Evidence is accumulating that indicates that the paracellular pathway is physiologically very important in divalent cation transport in the intestine (63–65). In addition, this pathway appears to be subject to regulation by various nutrients including Ca and Mg (65–67). What significance this has for Mg absorption remains to be determined. Characterization of the paracellular pathway may also shed some light on the interrelationship between Mg and Ca or P_i transport in the intestine.

LITERATURE CITED

1. Ebel, H. & Gunther, T. (1980) Magnesium metabolism: a review. J. Clin. Chem. Clin. Biochem. 18: 257–270.
2. Walser, M. (1967) Magnesium metabolism. Ergeb. Physiol. 59: 185–296.
3. Seelig, M. G. (1964) The requirements of magnesium by the normal adult. Am. J. Clin. Nutr. 14: 342–390.
4. Wilkinson, R. (1976) Calcium, phosphate, and magnesium absorption. In: Calcium, Phosphate, and Magnesium Metabolism (Nordin, B. E. C., ed.), pp. 96–112, Churchill Livingstone, Edinburgh.
5. Anast, C. S. & Gardner, D. W. (1981) Magnesium metabolism. In: Disorders of Mineral Metabolism (Bronner, F. & Coburn, J., eds), vol. 3, pp. 423–506, Academic Press, New York, NY.
6. Chutkow, J. G. (1964) Sites of magnesium absorption and excretion in the intestinal tract of the rat. J. Lab. Clin. Med. 63: 71–79.
7. Chutkow, J. G. (1966) Effect of magnesium deficiency on location of the intestinal absorption of magnesium in rats. Proc. Soc. Exp. Biol. Med. 123: 836–840.
8. Meneely, R., Leeper, L. & Ghishan, F. K. (1982) Intestinal maturation: in vivo magnesium transport. Pediatr. Res. 16: 295–298.
9. Aldor, T. A. M. & Moore, D. W. (1970) Magnesium absorption by everted sacs of rat intestine and colon. Gastroenterology 59: 745–753.
10. Urban, E. & Schedl, H. P. (1969) Net movements of magnesium and calcium in the rat small intestine in vivo. Proc. Soc. Exp. Biol. Med. 132: 1111–1113.
11. Behar, J. (1974) Magnesium absorption by the rat ileum and colon. Am. J. Physiol. 227: 334–340.
12. Ross, D. B. (1962) In vitro studies on the transport of magnesium across the intestinal wall of the rat. J. Physiol. 160: 417–428.
13. Roth, P. & Werner, E. (1979) Intestinal absorption of magnesium in man. Int. J. Appl. Radiat. Isot. 30: 523–526.
14. Danielson, B. G., Johansson, G., Jung, B., Ljunghall, S., Lundqvist, H. & Malmborg, P. (1979) Gastrointestinal magnesium absorption: kinetic studies with ^{28}Mg and a simple method for determination of fractional absorption. Miner. Electrolyte Metab. 2: 116–123.
15. Aikawa, J. K., Gordon, G. S. & Rhodes, E. L. (1960) Magnesium metabolism in human beings: studies with Mg^{28}. J. Appl. Physiol. 15: 503–507.
16. Graham, L. A., Caesae, J. J. & Burgen, A. S. V. (1960) Gastrointestinal absorption and excretion of Mg^{28} in man. Metabolism 9: 646–659.
17. Marshall, D. H., Nordin, B. E. C. & Speed, R. (1976) Calcium, phosphorus, and magnesium requirement. Proc. Nutr. Soc. 35: 163–173.
18. Brannan, O. B., Vergne-Marini, P., Pak, C. Y. C., Hull, A. R. & Fordtran, J. S. (1976) Magnesium absorption in the human small intestine: results in normal subjects, patients with chronic renal disease, and patients with absorptive hypercalciuria. J. Clin. Invest. 57: 1412–1418.
19. Hendrix, J. Z., Alcock, N. W. & Archibald, R. M. (1963) Competition between calcium, strontium, and magnesium for absorption in the isolated rat intestine. Clin. Chem. 9: 734–744.
20. Marcus, C. & Lengemann, F. (1962) Use of radioyttrium to study food movement in the small intestine of the rat. J. Nutr. 76: 179–182.
21. Behar, J. (1975) Effect of calcium on magnesium absorption. Am.

J. Physiol. 229: 1590–1595.
22. Dimich, A. & Wallach, S. (1969) Magnesium transport in humans with hypomagnesemia. J. Clin. Endocr. 29: 496–505.
23. Gaebel, G., Martens, H., Suendermann, M. & Galf, P. (1987) The effect of diet, intraruminal pH and osmolarity on sodium, chloride and magnesium absorption from the temporarily isolated and washed reticulo-rumen of sheep. Q. J. Exp. Physiol. 72: 501–511.
24. Martens, H. & Blume, I. (1986) Effect of intraruminal sodium and potassium concentrations and of the transmural potential difference on magnesium absorption from the temporarily isolated rumen of sheep. Q. J. Exp. Physiol. 71: 409–415.
25. Martens, H. & Harmeyer, J. (1985) Magnesium transport by isolated rumen epithelium of sheep. Res. Vet. Sci. 24: 161–165.
26. Martens, H. (1985) The effect of dinitrophenol on magnesium transport across an isolated preparation of sheep rumen epithelium. Q. J. Exp. Physiol. 70: 567–573.
27. Care, A. D., Brown, R. C., Farrar, A. R. & Pickard, D. W. (1984) Magnesium absorption from the digestive tract of sheep. Q. J. Exp. Physiol. 69: 577–587.
28. Scott, D. (1965) Factors influencing the secretion and absorption of calcium and magnesium in the small intestine of the sheep. Q. J. Exp. Physiol. 50: 312–329.
29. Care, A. D. & van't Klooster, A. T. (1965) In vivo transport of magnesium and other cations across the wall of the gastrointestinal tract of sheep. J. Physiol. (Lond.) 177: 174–191.
30. Wilson, T. H. & Wiesman, G. (1954) The use of sacs of everted small intestine for the study of the transference of substances from the mucosal to the serosal surface. J. Physiol. 123: 116–125.
31. Schachter, D., Dowdle, E. B. & Schenker, H. (1960) Active transport of calcium by the small intestine of the rat. Am. J. Physiol. 198: 263–268.
32. Anast, C., Kennedy, R., Volk, G. & Adamson, L. (1964) Studies of active transport of calcium, magnesium, and sulfate by the small intestine. J. Pediatr. 65: 1105 (abs.).
33. Levine, R. R., McNary, W. F., Kornguth, P. J. & LeBlanc, R. (1970) Histological reevaluation of everted gut technique for studying intestinal absorption. Eur. J. Pharmacol. 9: 211–219.
34. Plumb, J. A., Burston, D. A., Baker, T. G. & Garner, M. L. G. (1987) A comparison of the structural integrity of several commonly used preparations of rat small intestine in vitro. Clin. Sci. 73: 53–59.
35. Reddy, B. S. (1972) Studies on the mechanism of calcium and magnesium absorption in germfree rats. Arch. Biochem. Biophys. 149: 15–21.
36. Karbach, U. (1989) Cellular-mediated and diffusive magnesium transport across the descending colon of the rat. Gastroenterology 96: 1282–1289.
37. Levine, B. S., Brautbar, N., Walling, M. W., Lee, D. B. N. & Coburn, J. (1980) Effects of vitamin D and diet magnesium on magnesium metabolism. Am. J. Physiol. 239: E515–E523.
38. Hanna, S. (1961) Influence of large doses of vitamin D on magnesium metabolism in rats. Metabolism 10: 734–743.
39. Krejs, G. J., Nicar, M. J., Zerwekh, J. E., Norman, D. A., Kane, M. G. & Pak, C. Y. C. (1983) Effect of 1,25 dihydroxyvitamin D on calcium and magnesium absorption in the healthy human jejunum and ileum. Am. J. Med. 75: 973–976.
40. Meintzer, R. B. & Stenbock, H. (1955) Vitamin D and magnesium absorption. J. Nutr. 56: 285–294.
41. Anast, C. S. (1967) Magnesium studies in relation to vitamin D-resistant rickets. Pediatrics 40: 425–435.
42. Wilz, D. R., Gray, R. W., Dominguez, J. H. & Lemann, J. (1979) Plasma 1,25-$(OH)_2$-vitamin D concentrations and net intestinal calcium, phosphate, and magnesium absorption in humans. Am. J. Clin. Nutr. 32: 2052–2060.
43. Hodgkinson, A., Marshall, D. H. & Nordin, B. E. C. (1979) Vitamin D and magnesium absorption in man. Clin. Sci. 57: 121–123.
44. Brickman, A. S., Hartenbower, D. L., Norman, A. W. & Coburn, J. W. (1975) Action of 1,25$(OH)_2$ and 1 alpha(OH)vitamin D on magnesium metabolism in man. Clin. Res. 23: 315A (abs.).
45. Karbach, U. & Ewe, K. (1987) Calcium and magnesium transport and influence of 1,25-dihydroxyvitamin D_3. Digestion 37: 35–42.
46. Lifshitz, F., Harrison, H. C. & Harrison, H. E. (1967) Effects of vitamin D on magnesium metabolism in rats. Endocrinology 81: 849–853.
47. Heaton, F. W. & Parsons, F. M. (1961) The metabolic effect of high magnesium intake. Clin. Sci. 21: 273–284.
48. Richardson, J. A. & Welt, L. G. (1962) The hypomagnesemia of vitamin D administration. Proc. Soc. Exp. Biol. Med. 118: 512–514.
49. Clarkson, E. M., Warren, R. L., McDonald, S. J. & DeWardener, H. E. (1967) The effect of a high intake of calcium on magnesium metabolism in normal subjects and patients with chronic renal failure. Clin. Sci. 32: 11–18.
50. Norman, D. A., Fordtran, J. S., Brinkley, L. J., Zerwekh, J. E., Nicar, M. H., Strowig, S. M. & Pak, C. Y. C. (1981) Jejunal and ileal adaptation to alterations in dietary calcium: changes in calcium and magnesium absorption and pathogenic role of parathyroid hormone and 1,25-dihydroxyvitamin D. J. Clin. Invest. 67: 1599–1603.
51. Spencer, H., Lesniak, M., Kramer, L., Coffey, J. & Osis, D. (1980) Studies of magnesium metabolism in man. In: Magnesium in Health and Disease, pp. 911–919, Spectrum Publications, Jamaica, NY.
52. Leichsenring, J. M., Norris, L. M. & Lamison, S. A. (1951) Magnesium metabolism in college women: observations on the effect of calcium and phosphorus intake levels. J. Nutr. 45: 477–485.
53. Clark, I. (1969) Importance of dietary Ca:PO_4 ratios on skeletal, Ca, Mg, and PO_4 metabolism. Am. J. Physiol. 217: 865–870.
54. Ammann, P., Rizzoli, R. & Fleisch, H. (1986) Calcium absorption in rat large intestine in vivo: availability of dietary calcium. Am. J. Physiol. 251: G14–G18.
55. Alcock, N. & MacIntyre, I. (1962) Inter-relation between calcium and magnesium absorption. Clin. Sci. 22: 185–193.
56. Petith, M. M. & Schedl, H. P. (1977) Divalent cation transport by rat cecum and colon in calcium and magnesium deficiency. Proc. Soc. Exp. Biol. Med. 155: 225–229.
57. Krawitt, E. L. (1972) Effect of dietary magnesium deficiency on calcium transport by the rat small intestine. Proc. Soc. Exp. Biol. Med. 141: 569–572.
58. O'Dell, B. L., Morris, E. R. & Regan, W. O. (1960) Magnesium requirement of guinea pigs and rats: effect of calcium and phosphorus and symptoms of magnesium deficiency. J. Nutr. 70: 103–110.
59. Toothill, J. (1963) The effect of certain dietary factors on the apparent absorption of magnesium by the rat. Br. J. Nutr. 17: 125–134.
60. Hardwick, L. L., Clemens, R. A. & Jones, M. R. (1987) Effects of calcium phosphate supplementation on calcium, phosphorus, and magnesium metabolism in the Wistar rat. Nutr. Res. 7: 787–796.
61. O'Donnell, J. M. & Smith, M. W. (1973) Uptake of calcium and magnesium by rat duodenal mucosa analyzed by means of competing metals. J. Physiol. 229: 733–749.
62. Schachter, D. & Rosen, S. M. (1959) Active transport of ^{45}Ca by the small intestine and its dependence on vitamin D. Am. J. Physiol. 196: 357–362.
63. Wright, E. M. & Diamond, J. M. (1968) Effects of pH and polyvalent cations on the selective permeability of gall-bladder epithelium to monovalent ions. Biochim. Biophys. Acta 163: 57–74.
64. Fordtran, J. S., Morawski, S. G. & Santa Ana, C. A. (1985) Effect of magnesium on active and passive sodium transport in the human ileum. Gastroenterology 89: 1050–1053.
65. Smith, R. H. & McAllan, A. B. (1966) Binding of magnesium and calcium in the contents of the small intestine of the calf. Br. J. Nutr. 20: 703–718.
66. Tidball, C. S. (1964) Magnesium and calcium as regulators of intestinal permeability. Am. J. Physiol. 206: 243–246.
67. Cassidy, M. M. & Tidball, C. S. (1967) Cellular mechanism of

intestinal permeability: alterations produced by chelation depletion. J. Cell Biol. 32: 685–698.
68. Clark, I. & Rivera-Cordero, F. (1974) Effects of endogenous parathyroid hormone on calcium, magnesium and phosphate metabolism in rats. II. Alterations in dietary phosphate. Endocrinology 95: 360–369.
69. Bunce, G. E., Sauberlich, H. E., Reeves, P. G. & Oba, T. S. (1965) Dietary phosphorus and magnesium deficiency in the rat. J. Nutr. 86: 406–414.
70. Clark, I. (1968) Effects of magnesium ions on calcium and phosphorus metabolism. Am. J. Physiol. 214: 348–356.
71. Heaton, F. W., Hodgkinson, A. & Rose, G. A. (1964) Observations on the relation between calcium and magnesium metabolism in man. Clin. Sci. 27: 31–40.
72. Briscoe, A. M. & Ragan, C. (1966) Effect of magnesium on calcium metabolism in man. Am. J. Clin. Nutr. 19: 296–306.
73. Greger, J. L., Smith, S. A. & Snedeker, S. M. (1981) Effect of dietary calcium and phosphorus levels on the utilization of calcium, phosphorus, magnesium, manganese, and selenium by adult males. Nutr. Res. 1: 315–325.
74. Schwartz, R., Spencer, H. & Welsh, J. (1984) Magnesium absorption in human subjects from leafy vegetables, intrinsically labeled with stable ^{26}Mg. Am. J. Clin. Nutr. 39: 571–576.
75. Schwartz, R., Grunes, D., Wentworth, R. & Wein, E. (1980) Magnesium absorption from leafy vegetables intrinsically labeled with the stable isotope ^{26}Mg. J. Nutr. 110: 1365–1371.