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Ann. Rev. Pharmacol. Toxicol. 1977. 17:67–82
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PHARMACOLOGY OF MAGNESIUM

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In recent years, reliable and easy methods for the determination of magnesium in body fluids became available. This facilitated the investigative efforts on the various aspects of magnesium metabolism, and a large body of information has been accumulated in this field. However, two areas received greater attention; first, the hormonal and nonhormonal factors controlling the renal handling of magnesium and, second, the mechanisms of the hypocalcemia of magnesium depletion. The purpose of this report is to provide a review of the available data on these two aspects of the pharmacology of magnesium.

RENAL HANDLING OF MAGNESIUM

Each day, approximately 1800 mg of magnesium (Mg) is lost from plasma into the glomerulus but only 3–5% of filtered Mg is excreted in the urine. This conservation process is due to an effective tubular reabsorption of Mg. The normal concentration of Mg in blood is 1.7–2.2 mg/dl and is present in two forms. A diffusible fraction constitutes (75±9%, mean ± SD) of the total level; this fraction is filtered at the glomerulus, and a nondiffusible moiety is bound to protein. The relationship between these two forms follows the simple mass action equilibrium.

Characteristics of Renal Tubular Reabsorption of Magnesium

The concentration of Mg in the urine under diuretic conditions is lower than its concentration in glomerular filtrate, suggesting that Mg is actively transported by the nephron. However, it is not known whether active reabsorption occurs throughout the nephron. In studies carried out in the dog, the major portion of filtered Mg is reabsorbed by the proximal tubule and the reabsorption is isotonic or nearly so (1). A constant tubular fluid/ultrafiltrable (TF/UF) Mg ratio at unity in the proxi-

mal tubule could be interpreted to indicate passive Mg reabsorption at this site. This is based on the assumption that the transtubular potential difference is zero. Under such conditions Mg may leave the tubular lumen with the bulk flow of fluid secondary to active sodium reabsorption. If a small negative potential of less than –5 mv exists in the proximal tubule, active reabsorption of Mg cannot be ruled out. Furthermore, the significant fall in TF/UF Mg to a value below 1.0 during saline infusion suggests that active reabsorption of Mg may exist in the proximal tubule. Micropuncture data obtained from nondiuretic rats and from Psammomys indicate that the concentration of Mg in tubular fluid increases along the proximal tubule (2–4); in the Psammomys, for example, the TF/UF Mg in late proximal tubule is 1.52±0.44 (SD). These observations suggest that in the rat and Psammomys, magnesium is less reabsorbable in proximal tubule than in the dog.

Both micropuncture studies (4,5) and stop-flow experiments (6) demonstrate tubular fluid/plasma ratios of Mg which are well below 1.0, despite an electrical potential difference across the tubule which should lead to the appearance of greater concentration of Mg in the urine than in ultrafiltrate of plasma. These observations suggest that a very active transport mechanism for Mg exists in the distal nephron (5).

The fraction of filtered Mg excreted in the urine is significantly higher than that of calcium or sodium. Since, in the dog, the reabsorptions of sodium (7), calcium (8), and Mg (1) are isotonic in the proximal tubule, one must assume that Mg reabsorption in the distal nephron is dissociated from that of calcium or sodium or that Mg is secreted at these distal sites. In the rat, however, the difference in the proximal reabsorption of these ions may also contribute for the higher fraction of filtered Mg excretion.

Available data regarding Mg secretion by the renal tubule are contradictory. There is evidence that magnesium is secreted by the renal tubule of the aglomerular fish (9). Magnesium secretion by the kidney of the rat following prolonged Mg loading was demonstrated by Averill & Heaton (10), but Alfredson & Walser (11) were unable to confirm this observation. Chickens show no evidence for renal Mg secretion following the injection of Mg into the portal circulation (12). In studies carried out in the dog in our laboratory, Mg excretion did not exceed the filtered load during the infusions of large amounts of $MgCl^2$ (13); moreover, even when factors known to decrease tubular Mg reabsorption, such as saline infusion (14), calcium infusion (15), and chronic DOCA treatment (16), were superimposed on Mg loading, the fraction of filtered Mg excreted did not exceed unity (13). In contrast, others found that urinary Mg may reach values which are 10–20% greater than filtered Mg during the concomitant administration of Mg salts, saline, and furosemide to the dog (17). It appears, therefore, that if Mg secretion by the nephron exists, it plays a minor role in the renal handling of magnesium.

Thus, at least in the dog, the higher fractional excretion of Mg relative to that of sodium is not due to Mg secretion but rather to differences in their reabsorption at nephron sites distal to the proximal tubule. The micropuncture data of Wen, Evanson & Dirks (5) suggest that the loop of Henle is the site where the dissociation between the reabsorption of these two ions occur. Apparently Mg is less well

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reabsorbed at this site. The studies of De Rouffignac et al in the Psammomys indicate that Mg is added to the tubular fluid in the descending limb of the loop of Henle and reabsorbed in the ascending limb and, hence, a medullary recycling exists for Mg (4). Data from micropuncture experiments during acute Mg loading in rats support the existence of such recycling of Mg (18).

Many observations indicate that a limited capacity for tubular reabsorption of Mg exists. Thus, Averill & Heaton assert that Mg reabsorption is maximal in the rat when plasma level is close to normal (10), and observations of Knippers & Hehl in the dog suggest that Mg reabsorption becomes maximal when plasma levels reach 4 times the normal value (19). Our studies in the dog revealed that Mg reabsorption increased two- to threefold to reach a maximum as the filtered load was gradually raised (13). These data demonstrate a maximal tubular reabsorptive capacity for Mg (T_m Mg) in the dog of approximately 140 μg/min/kg body weight (Figure 1). There was a marked degree of splay, and the full capacity for Mg reabsorption was not observed until the filtered load was approximately twice the T_m value, suggesting a wide heterogeneity in the capacity of individual nephrons to reabsorb Mg. Moreover, the T_m Mg was significantly reduced by extracellular volume expansion, produced either by saline infusion or by the chronic administration of DOCA, and following the infusion of calcium (13).

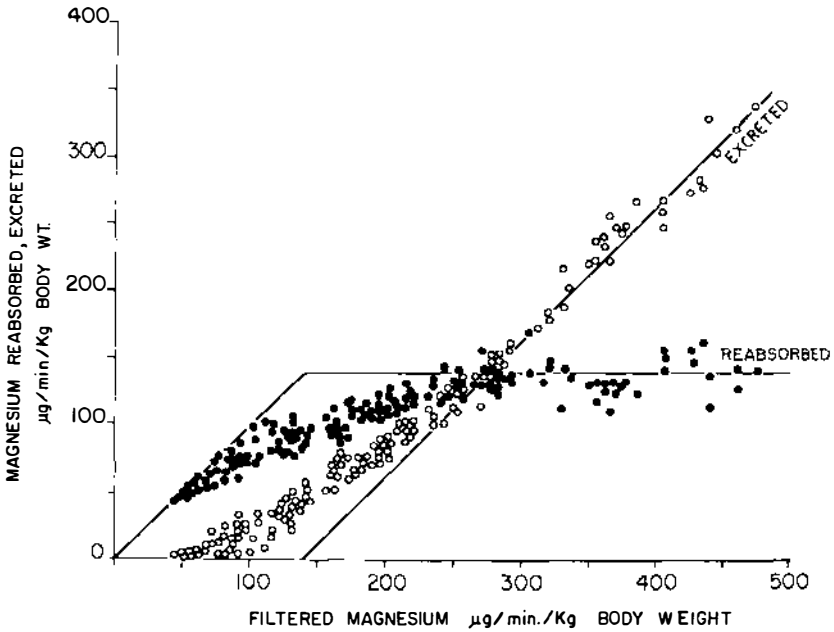

Figure 1 Relationship between quantity of magnesium filtered through glomeruli and quantities reabsorbed by renal tubule and excreted in urine during $MgCl_2$ infusion [Reprinted, by permission, from Massry et al (13)].

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Factors Controlling Urinary Excretion of Magnesium

CHANGES IN FILTERED LOAD An augmentation in the urinary excretion of Mg could occur following an increase in filtered load of these ions, a decrease in its tubular reabsorption, or both. An increase in filtered load of Mg could be produced by a rise in glomerular filtration rate (GFR) and/or an elevation in the concentration of Mg in blood; the effect of such increments in filtered loads on urinary Mg depends on how they are produced. Massry & Kleeman (20) found that a significant augmentation in filtered loads of magnesium induced by acute rise in GFR is associated with small increments in urinary Mg and sodium. These observations are consistent with the existence of glomerular tubular balance for Mg and follows that of sodium. It should be emphasized that a chronic rise in GFR may cause a significant loss of Mg. If the modest increments in the excretion of Mg observed during the acute rise in GFR were to continue over a long period of time, a considerable amount of Mg would be eliminated in the urine. An increase in filtered load of Mg by elevating its concentration in blood results in a marked rise in urinary Mg (13). The absolute quantity of Mg reabsorbed increases during hypermagnesemia, and when T_m Mg is reached, all the excess filtered load of Mg is quantitatively excreted in the urine. Therefore, hypermagnesemia is associated with magnesuria.

CHANGES IN TUBULAR REABSORPTION There are numerous hormonal and nonhormonal factors that influence the urinary excretion of Mg by altering its tubular reabsorption. These are listed in Table 1.

Extracellular fluid volume expansion Extracellular fluid volume expansion (ECVE) produced by the infusion of saline increases the excretion of Mg (1, 14). The magnesuria of ECVE occurred despite a significant reduction in its filtered loads, suggesting that ECVE with saline infusion depresses tubular reabsorption of

Table 1 Factors affecting tubular reabsorption of magnesium

Factors that decrease tubular reabsorption
Extracellular fluid volume expansion
Renal vasodilatation
Osmotic diuresis
Diuretic agents
Cardiac glycosides
Hypercalcemia
Alcohol ingestion
High sodium intake
Growth hormone
Thyroid hormone
Calcitonin
Chronic mineralocorticoid effect
Factors that enhance tubular reabsorption
Parathyroid hormone

Mg (14). Indeed, micropuncture studies demonstrated that ECVE inhibits the reabsorption of Mg in the proximal tubule (1).

Renal vasodilatation Gonda et al (21), Ahumada & Massry (22), and Thompson, Kaufman & DiScala (23) found that renal vasodilatation produced by the infusion of acetylcholine or bradykinin into the renal artery, with and without the intravenous administration of angiotensin, augments the urinary excretion of Mg, probably as a result of a decreased tubular reabsorption. The slope for the relationship between the clearance of Mg and that of sodium was 1.90, a value similar to that of 1.88 seen during saline infusion.

Osmotic diuresis Osmotic agents such as mannitol, glucose, and urea inhibit the tubular reabsorption of Mg and augment its urinary excretion (24–26). This inhibition is due to the decrease in the concentration of Mg in tubular fluid secondary to the inhibition of water reabsorption in excess of sodium.

Diuretics The administration of mercurial diuretics, furosemide or ethacrynic acid, causes an increase in the urinary excretion of Mg (26–28). Although these agents may have some action in the proximal tubule, they primarily inhibit tubular transport in the ascending limb of the loop of Henle (29). The acute administration of thiazides to the dog produces either no change (27) or a modest increase in Mg clearance (30). In humans, this drug causes an increase in Mg excretion for one or two days with subsequent return to baseline level (31). In contrast to the hypocalciuria which follows chronic thiazide administration (31–33), hypomagnesuria does not develop. Acetazolamide (Diamox®), a diuretic that augments sodium excretion by inhibiting carbonic anhydrase and reducing sodium reabsorption mediated by Na^+–H^+ exchange, produces either a fall or no change in Mg excretion in humans and in the intact dog (34–36). These observations suggest that sodium reabsorption which is coupled with Na^+–H^+ exchange is not linked with Mg transport. Further support for such a contention is provided by an experiment carried out in our laboratory (36) in which sodium diuresis was produced by the infusion of potassium salts which inhibit Na^+–H^+ exchange by causing intracellular alkalosis. There was no increase in urinary Mg accompanying the natriuresis observed during the potassium infusion.

Diet The ingestion of glucose or other rapidly metabolizable substances results in an increase in urinary Mg excretion with little or no augmentation in sodium excretion (37, 38). The magnesuria following glucose ingestion is due to a reduction in tubular reabsorption (39). The intake of fat has no effect on urinary Mg (38). The ingestion of 30–45 ml of ethanol produces a prompt increase in urinary Mg with no natriuresis in both normal subjects and chronic alcoholics (40, 41). This effect appears within 20 min after the alcohol ingestion and reaches a maximum in 60–90 min. The mechanism for this response is not clear, but it may represent another example of the effect of ingestion of rapidly metabolizable substrate (38).

A striking relationship exists between Mg intake and the urinary excretion of this ion. The ingestion of a diet deficient in Mg results in the disappearance of this ion

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from the urine, both in growing and adult animals (42, 43), and in humans (44). Urinary Mg is augmented with high Mg intake (45). Variations in salt intake in humans may be accompanied by concomitant changes in Mg excretion (46). Spontaneous hypercalcemia or that produced by calcium infusion is associated with magnesuria as a result of inhibition of tubular Mg reabsorption (15).

During starvation for periods up to 60 days, there is a continued urinary excretion of substantial amounts of Mg (47). These urinary losses are associated with a reduced content of Mg in muscle but a very small fall in serum Mg. Sodium excretion may average 50–120 meq/day during the first week of fasting and decreases thereafter, to 5–120 meq/day. These observations suggest decreased tubular reabsorption of these two ions, although the site in the nephron where this occurs is not delineated as yet. The administration of small quantities of sodium (40 meq/day) during prolonged fasting causes a marked increase in the urinary excretion of Mg (48). Refeeding with even small amounts of glucose is followed by a rapid reduction in urinary sodium and Mg (47).

Parathyroid hormone In contrast to the well-established effect of parathyroid hormone (PTH) on renal handling of calcium, the influence of PTH on Mg excretion appears to be less well defined. Heaton (49) reported that administration of PTH increases Mg excretion in rats. However, these animals were hypercalcemic, and hypercalcemia augments urinary Mg independent of PTH (15). In contrast, MacIntyre, Boss & Troughton found a decrease in Mg excretion in rats receiving PTH (50). We have evaluated the influence of PTH on the renal handling of Mg in dogs receiving infusions of Mg (13). In every animal, the intramuscular injection of parathyroid extract decreased fractional Mg excretion. In studies carried out in patients with hypoparathyroidism, Bethune, Turpin & Inoue (51) found a reduction in urinary Mg excretion following the repeated intramuscular injection of parathyroid extract. In humans with hyperparathyroidism, serum Mg levels have been reported to be low with normal or even high urinary Mg excretion (52–54). These observations are not necessarily contradictory in that the hypercalcemia which is present may inhibit the reabsorption of magnesium and overcome the effect of parathyroid hormone.

Adrenal steroids Urinary Mg may be augmented under the influence of glucocorticoids (46) and urinary Mg losses are increased in patients with Cushing's syndrome. Massry et al (55) reported that the acute administration of methylprednisolone to adrenalectomized dogs does not increase the urinary excretion of Mg. In normal humans, Lemann, Piering & Lennon (56) gave cortisol and found no change in urinary Mg.

The acute administration of mineralocorticoids has no effect on magnesium excretion in dogs or man (55, 56). Thus, the mechanisms for sodium transport, which are stimulated by mineralocorticoids in the distal tubule, are dissociated from the transport of Mg. Certain clinical and experimental data suggest that the excretion of Mg may be affected by long-term action of mineralocorticoids. Thus, Scott & Dobson described an increase in Mg excretion in sheep following prolonged aldosterone administration (57). In primary aldosteronism, hypomagnesemia and a high

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renal clearance of Mg have been reported (58). These observations suggest that there is a difference between the acute and the long-term action of mineralocorticoids on the renal handling of Mg. Massry et al (16) have studied the effect of long-term administration of DOCA on urinary excretion of Mg in dogs. They found that sodium excretion fell on the first day of DOCA treatment and then returned to baseline values. In contrast, urinary Mg remained unchanged until the second or third day of DOCA administration, when it increased progressively to exceed control levels by two- to fivefold (Figure 2). When similar studies were carried out in dogs fed a sodium-free diet, there were no changes in Mg excretion during the administration of DOCA (Figure 3). Suki and co-workers have reported similar results in rats given mineralocorticoids (59). The initial sodium retention that occurs during prolonged mineralocorticoid administration induces extracellular volume expansion which may lead to escape from the hormonal effect on sodium excretion (60). Extracellular volume expansion produces a decrease in the proximal tubular

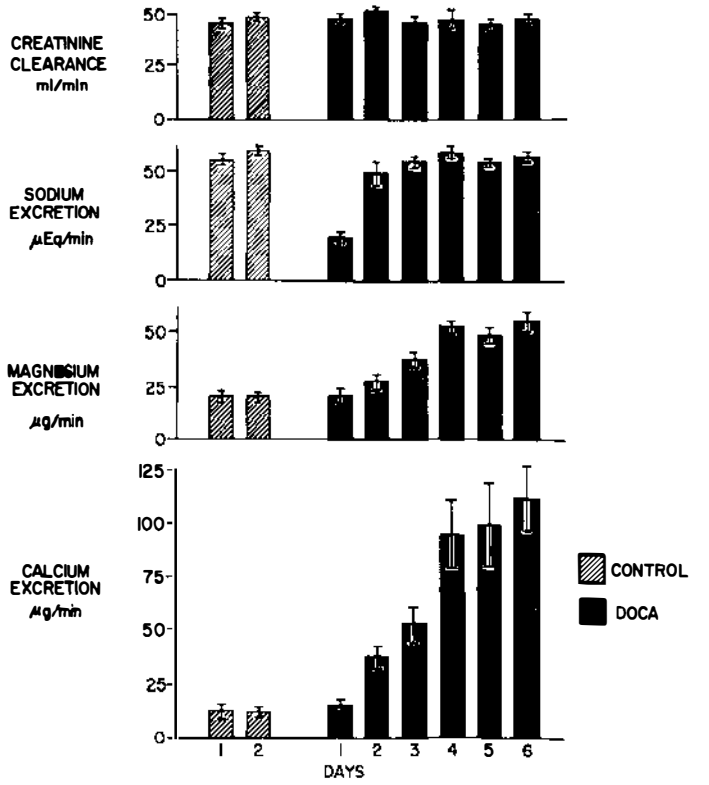

Figure 2 The changes (mean ± SE) in the excretion of sodium, magnesium, and calcium observed in 6 dogs receiving liberal sodium intake and 20 mg of desoxycorticosterone acetate per day over 6 successive days [Reprinted, by permission, from Massry et al (16)].

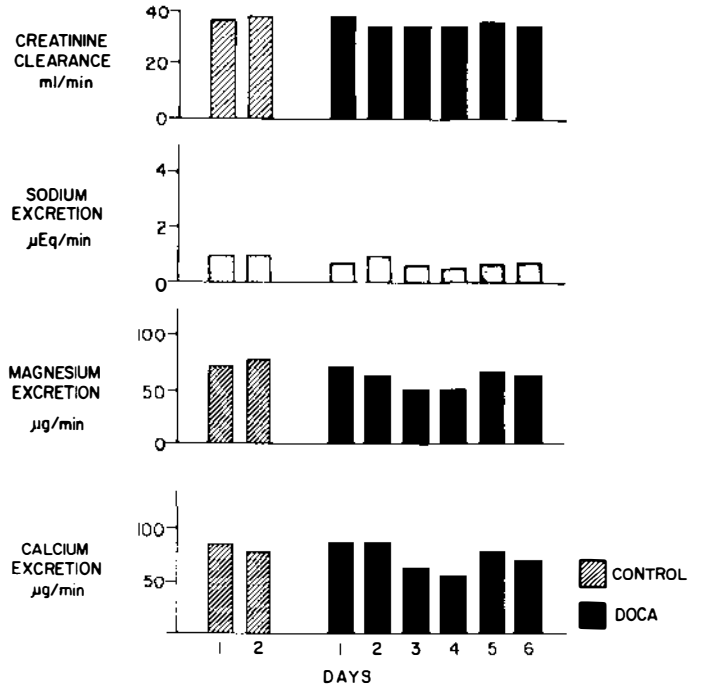

Figure 3 The changes (mean ± SE) in the excretion of sodium, magnesium, and calcium observed in 6 dogs receiving sodium-free diet and 20 mg of desoxycorticosterone acetate per day over 6 successive days.

reabsorption of sodium and Mg, which enhances the delivery of these ions to the distal segment of the nephron where mineralocorticoids may promote sodium reabsorption without a direct effect on Mg transport. The net result would be an increase in the excretion of Mg only. Other data suggest that a decrease in reabsorption in the distal nephron may also contribute to the increase in the excretion of Mg during the escape from the effect of mineralocorticoids (61).

Thyroid hormone The effect of altered states of thyroid function on Mg metabolism has been studied by Jones and co-workers (62) and Rizek, Dimick, & Wallach (63). They found decreased serum Mg levels and increased urinary excretion of Mg in patients with hyperthyroidism, while those with hypothyroidism had elevated plasma levels and decreased urinary excretion. After treatment of either condition, plasma levels shifted toward normal and urinary excretion of Mg increased in patients with hypoparathyroidism.

Other hormones The effect of calcitonin on urinary Mg is variable. The administration of this hormone decreased urinary Mg in the rat (64). In humans, Mg excretion either increased (65) or remained unchanged (66). Growth hormone appears to have

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an effect on the renal handling of Mg, opposite to that of PTH; thus, the administration of growth hormone results in increased urinary excretion of Mg (67).

HYPOCALCEMIA OF MAGNESIUM DEPLETION

Hypocalcemia has been reported with magnesium depletion in a number of species, including chicks (68), rats receiving a low calcium intake (69, 70), sheep (71), pigs (72), calves (73, 74), dogs (75), monkeys (76), and humans (77–81). Although the occurrence of hypocalcemia during magnesium depletion seems well established, the mechanisms underlying this phenomenon are not well understood. Theoretically, several factors should be responsible for the hypocalcemia. These include (*a*) decreased responsiveness of the skeleton to parathyroid hormone, (*b*) failure of parathyroid hormone production by the parathyroid glands, (*c*) inhibition of release of parathyroid hormone from the glands, (*d*) augmented action or secretion of calcitonin, (*e*) increased urinary losses of calcium, (*f*) reduced gastrointestinal absorption of calcium, and (*g*) altered equilibrium for calcium between bone and extracellular fluid favoring calcium retention or deposition in bone.

Skeletal Resistance to the Calcemic Action of the Parathyroid Hormone

Considerable evidence exists suggesting that magnesium depletion may be associated with unresponsiveness to PTH (69, 77–82), although some investigators did not find such an abnormality (70, 75, 76, 83–87). Estep et al (77), Muldowney and co-workers (79), and Woodward, Webster & Carr (81) found no calcemic response to parathyroid extract administration in patients with hypomagnesemia due to chronic alcoholism, steatorrhea, or severe diarrhea. In most of these patients, the administration of magnesium alone restored the responsiveness to parathyroid extract. Connor et al (80) reported a patient with magnesium depletion secondary to malabsorption; hypocalcemia improved after administration of parathyroid extract but the response was markedly reduced when compared to the effect observed after magnesium repletion. On the other hand, Salet et al (83), Paunier et al (84), and Stromme et al (85) reported an increase in serum calcium after parathyroid extract administration in infants with hypomagnesemia and concluded that there was normal responsiveness to parathyroid extract. Similar observations were reported recently in a child with primary hypomagnesemia (87). These reports led Hahn, Chase & Avioli (70) and Suh et al (87) to suggest that factors other than magnesium depletion might have accounted for unresponsiveness of the skeleton to parathyroid hormone in the patients with alcoholism or malabsorption. Careful evaluation of the data obtained in the hypomagnesemic infants revealed that the response to parathyroid extract was delayed, that seven doses of the extract were required to produce a significant rise in serum calcium in the case of Paunier et al (84), and, that the calcemic response to PTE was markedly reduced in the case of Salet et al (83) when compared with the response after magnesium repletion. Moreover, the patients of Stromme et al had received parenteral magnesium up until a few days before treatment with parathyroid extract, and the serum magnesium was 1.1 mg/100 ml at the time of study (85); it is likely that the degree of magnesium deficiency was mild, accounting for the prompt calcemic response to parathyroid extract.

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In the chick, magnesium depletion is associated with marked hypocalcemia which is unresponsive to the administration of parathyroid extract (68). In magnesium-depleted rats, MacManus, Heaton & Lucas reported data from experiments carried out both in vitro and in vivo showing skeletal unresponsiveness to parathyroid extract (69). On the other hand, Hahn and co-workers found similar increments in serum calcium and urinary excretion of hydroxyproline in both normal and magnesium-depleted rats (70). The discrepancies between these results may be related to the degree of magnesium depletion and/or hypomagnesemia; in the studies of MacManus et al (69), the mean value for serum magnesium was 0.46 ± 0.03 (SE) mg/100 ml (29% of control), while the mean serum magnesium was 0.95 ± 0.5 mg/100 ml (58% of control) in the magnesium-depleted rats of Hahn et al (70).

Levi et al (82) found that magnesium depletion is associated with reduced calcemic response to parathyroid extract in adult dogs when this is evaluated after a 7-hr infusion of the exogenous hormone; magnesium repletion completely restored the calcemic response to parathyroid extract (Figure 4). In contrast, Suh, Csima & Fraser evaluated the effect of parathyroid extract on serum calcium in growing puppies with magnesium depletion (75). They found that the changes in serum calcium in magnesium-depleted puppies after 17–48 hours of parathyroid extract infusion were not different from those observed in control animals; they suggested that unresponsiveness of the skeleton to PTH was not responsible for the hypocalcemia in the magnesium-depleted puppies. It is possible that the differences between the results of Suh et al (75) and those of Levi et al (82) are related to the age of the dogs or to the duration of the infusion of the parathyroid extract.

Dunn administered parathyroid extract to monkeys both before and after magnesium depletion and found no significant difference between the changes in serum calcium (76). These results are difficult to reconcile with other reported data; how-

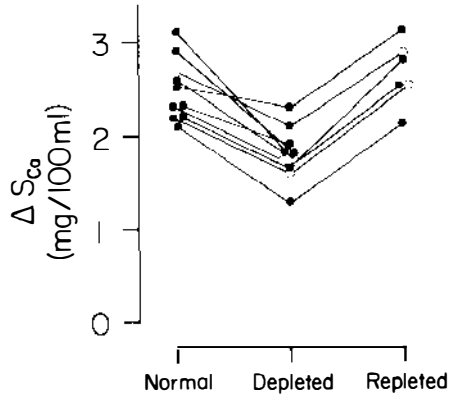

Figure 4 The changes in serum calcium (Δ SCa) induced by the infusion of parathyroid extract in the normal animals, during magnesium-depleted state and after magnesium repletion. *Open circles* represent the mean of two studies in the same animal, and the *lines* connect data in the same dog [Reprinted, by permission, from Levi et al (82)].

ever, there may be species differences in the response to parathyroid extract during magnesium depletion.

Function of Parathyroid Glands

Despite the reduced calcemic response to parathyroid extract in the study of Levi et al (82), serum calcium was either normal or slightly elevated after the infusion of the extract. This finding suggested that the spontaneous hypocalcemia observed in these animals would not have occurred had there been adequate secretion of endogenous parathyroid hormone. It is possible that complete or partial failure of parathyroid hormone secretion during magnesium depletion is an important factor leading to the initial appearance of hypocalcemia. Indeed, Levi et al (82) found that the blood levels of parathyroid hormone were not elevated during magnesium depletion despite the hypocalcemia, suggesting impaired function of the parathyroid glands. Anast and co-workers (86) and Suh et al (87) each found a reduced or undetectable plasma level of immunoreactive parathyroid hormone in separate patients with magnesium depletion. A similar finding was reported by Chase & Slatopolsky (88). In addition, studies by Targovnik, Rodman & Sherwood (89) showed that the release of parathyroid hormone from parathyroid glands in vitro was markedly reduced when magnesium concentration in the media was below 0.70 mg/dl. These findings are not necessarily inconsistent with data showing that acute reduction in the concentration of magnesium in blood perfusing the parathyroid glands causes increased release of parathyroid hormone (90). Chronic hypomagnesemia may have a different effect on parathyroid gland metabolism, and this effect may depend on the degree of hypomagnesemia. There is evidence that parathyroid gland activity may be normal or increased during magnesium deficiency. Thus, Sherwood (91) and Connor et al (80) each reported elevated circulating levels of parathyroid hormone in an individual patient with magnesium depletion, and parathyroid hyperplasia has been reported in calves with magnesium deficiency (74). However, even when the levels of parathyroid hormone are elevated during magnesium depletion, they may not represent an adequate or appropriate response of the parathyroid glands for the degree of hypocalcemia.

Recent observations by Anast and associates (92) and Rude and co-workers (93) indicate that marked magnesium deficiency may inhibit the release of PTH from the parathyroid glands. They found that blood levels of PTH increased markedly within one minute of the administration of magnesium. These observations are consistent with in vitro studies showing that low magnesium concentration in the incubation media diminished the secretion of PTH (89) but not its synthesis (94) by bovine parathyroid glands.

Equilibrium Between Calcium in Extracellular Fluid and Bone

During magnesium depletion, an altered equilibrium may exist between the calcium in extracellular fluid and bone, and such a disturbance may contribute to the hypocalcemia. Neuman & Neuman postulated that magnesium ion may exchange for calcium on the bone surface (95). MacManus & Heaton found that the calcium released from bone, in vitro, by both physicochemical processes and metabolic

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activity was dependent upon the magnesium concentration in the incubation media (96). Similar observations have been reported by Pak & Diller (97). It is possible that, in the intact animal, magnesium depletion may both reduce the release of calcium from the bone surface and exert an inhibitory effect on normal process of bone resorption; moreover, a defective action of parathyroid hormone on bone may be, at least in part, a consequence of such interrelationships between magnesium and bone. The hypocalcemia, itself, could be a factor preventing a skeletal response to PTE (98,99), possibly as a result of the presence of excess osteoid (99). Indeed, the presence of excess osteoid has been found in magnesium-deficient chicks (68).

Other Factors

Although it is possible that decreased gastrointestinal absorption of calcium, enhanced urinary excretion of calcium, or increased release of calcitonin could be responsible for the hypocalcemia, all available data make these possibilities remote. Thus, during magnesium depletion, calcium absorption is either not impaired or increased (68,100–103), and urinary calcium is low (78,104). An increase in the secretion of calcitonin during magnesium depletion seems unlikely. Elevated levels of magnesium may stimulate the release of calcitonin in the rat (105), although perfusion of the goat thyroid with hypermagnesemic blood did not alter calcitonin secretion (106). Moreover, thyroidectomy and thyroparathyroidectomy failed to alter the hypocalcemia seen with magnesium depletion (75, 76) suggesting that calcitonin is not of importance. Finally, Suh et al (87) did not find an elevation in the blood levels of calcitonin during hypomagnesemia.

SUMMARY

The available data, therefore, indicate that the factors responsible for the hypocalcemia in magnesium deficiency are multiple. Relative or complete failure of the function of parathyroid glands, inhibition of release of parathyroid hormone from the glands, impaired skeletal response to parathyroid hormone, and abnormalities in the equilibrium between bone and extracellular fluid may each or all be operative in various species.

Literature Cited

1. Brunette, M., Wen, S. F., Evanson, R. L., Dirks, J. H. 1969. Micropuncture study of magnesium reabsorption in the proximal tubule of the dog. *Am. J. Physiol.* 216:1510–16
2. LeGrimellec, C., Roinel, N., Morel, F. 1973. Simultaneous Mg, Ca, P, K, Na, and Cl analysis in rat tubular fluid. I. During perfusion of either inulin or ferrocyanide. *Pfluegers Arch.* 340:181–96
3. Morel, F., Roinel, N., LeGrimellec, C. 1969. Electron probe analysis of tubular fluid composition. *Nephron* 6:350–64
4. DeRouffignac, C., Morel, F., Moss, N., Roinel, N. 1973. Micropuncture study of water and electrolyte movements along the loop of Henle in Psammomys with special reference to magnesium, calcium and phosphorus. *Pfluegers Arch.* 344:309–26
5. Wen, S. F., Evanson, R. L., Dirks, J. H. 1970. Micropuncture study of magnesium transport in proximal and distal tubule of the dog. *Am. J. Physiol.* 219:570–76
6. Samiy, A. H. E., Brown, J. L., Globus, D. L., Kessler, R. H., Thompson, D. D. 1960. Interrelations between renal transport system of magnesium and calcium. *Am. J. Physiol.* 189:559–602

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7. Bennett, C. M., Clapp, J. R., Berliner, R. W. 1967. Micropuncture study of the proximal and distal tubule in the dog. *Am. J. Physiol.* 213:1254–62
8. Duarte, C. G., Watson, J. F. 1967. Calcium reabsorption in proximal tubule of the dog nephron. *Am. J. Physiol.* 212:1355–60
9. Berglund, F., Forster, R. P. 1958. Renal tubular transport of inorganic divalent ions by the aglomerular marine teleost, Lophius Americanus. *J. Gen. Physiol.* 41:429–40
10. Averill, C. M., Heaton, F. W. 1960. The renal handling of magnesium. *Clin. Sci.* 31:353–60
11. Alfredson, K. S., Walser, M. 1970. Is magnesium secreted by the rat renal tubule? *Nephron* 7:242–47
12. Robinson, R. R., Postwood, R. M. 1962. Mechanism of magnesium excretion by the chick. *Am. J. Physiol.* 202:309–12
13. Massry, S. G., Coburn, J. W., Kleeman, C. R. 1969. Renal handling of magnesium in the dog. *Am. J. Physiol.* 216:1460–67
14. Massry, S. G., Coburn, J. W., Chapman, L. W., Kleeman, C. R. 1967. Effect of NaCl infusion on urinary CA^{++} and Mg^{++} during reduction in their filtered load. *Am. J. Physiol.* 213:1218–24
15. Coburn, J. W., Massry, S. G., Kleeman, C. R. 1970. The effect of calcium infusion on renal handling of magnesium with normal and reduced glomerular filtration rate. *Nephron* 7:131–43
16. Massry, S. G., Coburn, J. W., Chapman, L. W., Kleeman, C. R. 1968. The effect of long-term desoxycorticosterone acetate administration on the renal excretion of calcium and magnesium. *J. Lab. Clin. Med.* 71:212–19
17. Wen, S. F., Wong, N. L., Dirks, J. H. 1971. Evidence for renal magnesium secretion during magnesium infusion in the dog. *Am. J. Physiol.* 220:33–37
18. LeGrimellec, C., Roinel, N., Morel, F. 1973. Simultaneous Mg, Ca, P, K, Na and Cl analysis in rat tubular fluid. II. During acute Mg plasma loading. *Pfluegers Arch.* 340:197–210
19. Knippers, R., Hehl, U. 1965. Die renale Ausscheidung von Magnesium, Calcium, und Kalium nach Erhohung der Magnesium Kenzentration in Plasma des Hundes. *Z. Gesamte Exp. Med.* 139:154–65
20. Massry, S. G., Kleeman, C. R. 1972. Calcium and magnesium excretion during acute rise in glomerular filtration rate. *J. Lab. Clin. Med.* 80:654–64
21. Gonda, A., Wong, N., Seely, J. F., Dirks, J. H. 1969. The role of hemodynamic factors on urinary calcium and magnesium excretion. *Can. J. Physiol. Pharmacol.* 47:619–26
22. Ahumada, J. J., Massry, S. G. 1971. Renal vasodilatation: Effect on renal handling of phosphate. *Clin. Sci.* 41: 109–21
23. Thompson, R. B., Kaufman, C. E., DiScala, V. A. 1971. Effect of renal vasodilatation on divalent ion excretion and Tm PAH in anesthetized dogs. *Am. J. Physiol.* 221:1097–1104
24. Better, O. S., Gonick, H. C., Chapman, L. C., Varrady, P. D., Kleeman, C. R. 1966. Effect of urea-saline diuresis on renal clearance of calcium, magnesium, and inorganic phosphate in man. *Proc. Soc. Exp. Biol. Med.* 121:592–96
25. Wesson, L. G. Jr. 1962. Magnesium, calcium and phosphate excretion during osmotic diuresis in the dog. *J. Lab. Clin. Med.* 60:422–33
26. Parfitt, A. M. 1969. The acute effects of mersalyl, chlorothiazide, and mannitol on the renal excretion of calcium and other ions in man. *Clin. Sci.* 36:267–82
27. Eknoyan, G., Suki, W. N., Martinez-Maldonado, M. 1970. Effect of diuretics on urinary excretion of phosphate, calcium, and magnesium in thyroparathyroidectomized dog. *J. Lab. Clin. Med.* 76:257–66
28. Walser, M. 1967. Magnesium metabolism. *Ergeb. Physiol. Biol. Chem. Exp. Pharmakol.* 59:185–296
29. Seldin, D. W., Eknoyan, G., Suki, W. N., Rector, F. C. Jr. 1966. Localization of diuretic action from the pattern of water and electrolyte excretion. *Ann. NY Acad. Sci.* 139:328–43
30. Duarte, C. G., Bland, J. H. 1965. Calcium, phosphorus and uric acid clearances after intravenous administration of chlorothiazide. *Metabolism* 14:211–19
31. Parfitt, A. M. 1972. The interaction of thiazide diuretics with parathyroid hormone and vitamin D. Studies in patients with hypoparathyroidism. *J. Clin. Invest.* 51:1879–88
32. Brickman, A. S., Massry, S. G., Coburn, J. W. 1972. Changes in serum and urinary calcium during treatment with hydrochlorothiazide: Studies on mechanisms. *J. Clin. Invest.* 51:945–54
33. Yendt, E. R., Gagne, R. J. A., Cohanim, M. 1966. The effect of thiazides in

Annu. Rev. Pharmacol. Toxicol. 1977.17:67-82. Downloaded from www.annualreviews.org by Central College on 12/14/11. For personal use only.

idiopathic hypercalciuria. *Am. J. Med. Sci.* 251:449–60
34. Barker, E. S., Elkinton, J. R., Clark, J. K. 1959. Studies of the renal excretion of magnesium in man. *J. Clin. Invest.* 38:1733–45
35. Heidland, A., Rockel, A., Maidhof, R., Hennemann, H. 1970. Divergenz der Renalen Natrium und Magnesium Excretion nach Trometaniol (Trispuffer), Amerloride HCl, Acetazolemel und Parathormone ein Effekt der Harnalkalisierung? *Klin. Wochenschr.* 48: 371–74
36. Massry, S. G., Popovtzer, M. M., Chapman, L. W., Kleeman, C. R. 1968. Effect of potassium infusion and intravenous diamox on the interdependence between the renal handling of sodium, calcium, and magnesium. *Clin. Res.* 16:391 (Abstr.)
37. Hodgkinson, A., Heaton, F. W. 1965. The effect of food ingestion on the urinary excretion of calcium and magnesium. *Clin. Chim. Acta* 11:354–62
38. Lindeman, R. D., Adler, S., Yiengst, M. J., Beard, E. S. 1967. Influence of various nutrients on urinary divalent cation excretion. *J. Lab. Clin. Med.* 70:236–45
39. Lemann, J. Jr., Lennon, E. J., Piering, W. F., Prien, E. L. Jr., Ricanati, E. S. 1970. Evidence that glucose ingestion inhibits net tubular reabsorption of calcium and magnesium in man. *J. Lab. Clin. Med.* 75:578–85
40. McCollister, R. J., Prasad, A. S., Doe, R. P., Flink, E. B. 1958. Normal renal magnesium clearance and the effect of water loading, chlorothiazide and ethanol on magnesium excretion. *J. Lab. Clin. Med.* 52:928
41. Kalbfleisch, J. M., Lindeman, R. D., Ginn, H. E., Smith, W. O. 1963. Effects of ethanol administration on urinary excretion of magnesium and other electrolytes in alcoholic and normal subjects. *J. Clin. Invest.* 42:1471–75
42. Chutkow, J. G. 1965. Studies on the metabolism of magnesium in the magnesium deficient rat. *J. Lab. Clin. Med.* 75:912–26
43. Heaton, F. W. 1969. The kidney and magnesium homeostasis. *Ann. NY Acad. Sci.* 16:775–85
44. Barnes, B. A., Cope, O., Harrison, T. 1950. Magnesium conservation in the human being on low magenesium diet. *J. Clin. Invest.* 37:430–40
45. Heaton, F. W., Parson, F. M. 1961. The metabolic effect of high magnesium intake. *Clin. Sci.* 21:273–84
46. Hills, A. G., Parson, D. W., Webster, G. D. Jr., Rosenthal, O., Conover, H. 1959. Influence of the renal excretion of sodium chloride upon the renal excretion of magnesium and other ions by human subjects. *J. Clin. Endocrinol.* 19:1192–1211
47. Drenick, E. J. 1970. The effects of acute and prolonged fasting and refeeding on water, electrolyte, and acid-base metabolism. In *Clinical Disorders of Fluid and Electrolyte Metabolism,* ed. M. H. Maxwell, C. R. Kleeman, 1117–37. New York: McGraw-Hill
48. Brickman, A. S., Drenick, E. J., Fisher, J., Coburn, J. W. 1970. The effect of sodium supplementation on divalent cation excretion during prolonged fasting. *Clin. Res.* 18:183
49. Heaton, F. W. 1968. The parathyroid glands and magnesium metabolism in the rat. *Clin. Sci.* 28:543–53
50. MacIntyre, I., Boss, S., Troughton, V. A. 1963. Parathyroid hormone and magnesium homeostasis. *Nature* 198: 1058–60
51. Bethune, J. E., Turpin, R. A., Inoue, H. 1968. Effect of parathyroid hormone extract on divalent ion excretion in man. *J. Clin. Endocrinol Metab.* 28:673–78
52. Heaton, F. W., Pyrah, L. N. 1963. Magnesium metabolism in patients with parathyroid disorders. *Clin. Sci.* 25:475–85
53. King, R. G., Stanbury, S. W. 1970. Magnesium metabolism in primary hyperparathyroidism. *Clin. Sci.* 39: 281–303
54. Hanna, S., North, K. A. K., MacIntyre, I., Fraser, R. 1961. Magnesium metabolism in parathyroid disease. *Br. Med. J.* 2:1253–56
55. Massry, S. G., Coburn, J. W., Chapman, L. W., Kleeman, C. R. 1967. The acute effect of adrenal steroids on the interrelationship between the renal excretion sodium, calcium and magnesium. *J. Lab. Clin. Med.* 70:563–70
56. Lemann, J. Jr., Piering, W. F., Lennon, E. J. 1970. Studies of the acute effects of aldosterone and cortisol on the interrelationship between renal sodium, calcium and magnesium excretion in normal man. *Nephron* 7:117–30
57. Scott, D., Dobson, A. 1965. Aldosterone and the metabolism of magnesium and other minerals in sheep. *Q. J. Exp. Physiol.* 50:42–56
58. Horton, R., Bigliere, E. G. 1962. Effect of aldosterone on the metabolism of

Annu. Rev. Pharmacol. Toxicol. 1977.17:67-82. Downloaded from www.annualreviews.org by Central College on 12/14/11. For personal use only.

Mg. *J. Clin. Endocrinol Metab.* 22: 1187–92
59. Suki, W. N., Schwettmann, R. S., Rector, F. C. Jr., Seldin, D. W. 1968. Effect of chronic mineralocorticoid administration on calcium excretion in the rat. *Am. J. Physiol.* 215:71–74
60. August, T., Nelson, D. H., Thorn, G. W. 1958. Response of normal subjects to large amounts of aldosterone. *J. Clin. Invest.* 37:1549–55
61. Rasteger, A., Agus, Z. S., Connor, T. B., Goldberg, M. 1972. Renal handling of calcium and phosphate during mineralocorticoid "escape" in man. *Kidney Int.* 2:279–86
62. Jones, J. E., Desser, P. C., Shane, S. R., Flink, E. B. 1966. Magnesium metabolism in hyperthyroidism and hypothyroidism. *J. Clin. Invest.* 45:891–900
63. Rizek, J. E., Dimich, A., Wallach, S. 1965. Plasma and erythrocyte Mg in thyroid disease. *J. Clin. Endocrinol Metab.* 25:350–58
64. Aldred, J. P., Kleszynski, R. R., Basticen, J. W. 1970. Effects of acute administration of porcine and salman calcitonin on urine electrolyte excretion in rats. *Proc. Soc. Exp. Biol. Med.* 134:1175–80
65. Paillard, F., Ardaillou, R., Malendin, H., Fillastre, J. P., Prier, S. 1972. Renal effects of salmon calcitonin in man. *J. Lab. Clin. Med.* 80:200–16
66. Cochran, M., Peacock, M., Sacks, G., Nordin, B. E. C. 1970. Renal effects of calcitonin. *Br. Med. J.* 1:135–37
67. Hanna, S., Harrison, M. T., MacIntyre, I., Fraser, R. 1961. Effects of growth hormone on calcium and magnesium metabolism. *Br. Med. J.* 2:12–15
68. Reddy, C. R., Coburn, J. W., Hartenbower, D. L., Friedler, R. M., Brickman, A. S., Massry, S. G., Jowsey, J. 1973. Studies on mechanisms of hypocalcemia of magnesium depletion. *J. Clin. Invest.* 52:3000–10
69. MacManus, J., Heaton, F. W., Lucas, P. W. 1971. Decreased response to parathyroid hormone in magnesium deficiency. *J. Endocrinol.* 49:253–58
70. Hahn, T. J., Chase, L. R., Avioli, L. V. 1972. Effect of magnesium depletion on responsiveness to parathyroid hormone in parathyroidectomized rats. *J. Clin. Invest.* 51:886–91
71. L'Estrange, J. L., Axford, R. F. E. 1964. A study of magnesium and calcium metabolism in lactating ewes fed a semipurified diet low in magnesium. *J. Agric. Sci.* 63:353–68
72. Miller, E. R., Ullrey, D. E., Zutaut, C. L., Baltzer, B. V., Schmidt, D. A., Hoefer, J. A., Luecke, R. W. 1965. Magnesium requirement of the baby pig. *J. Nutr.* 85:13–20
73. Smith, R. H. 1961. Importance of magnesium in the control of plasma calcium in the calf. *Nature* 191:181–83
74. Larvor, P., Girard, A., Brochart, M. 1964. Experimental magnesium deficiency in the calf. II. Interference of magnesium deficiency with calcium metabolism. *Ann. Biol. Anim. Biochim. Biophys.* 4:371–82
75. Suh, S. M., Csima, A., Fraser, D. 1971. Pathogenesis of hypocalcemia in magnesium depletion. *J. Clin. Invest.* 50:2668–78
76. Dunn, M. J. 1971. Magnesium depletion in rhesus monkey: Induction of magnesium-dependent hypocalcemia. *Clin. Sci.* 41:333–43
77. Estep, H., Shaw, W. A., Watlington, C., Hobe, R., Holland, W., Tucker, S. G. 1969. *J. Clin. Endocrinol.* 29:842–48
78. Shills, M. E. 1969. Experimental human magnesium depletion. *Medicine* 48:61–85
79. Muldowney, F. P., McKenna, T. J., Kyle, L. H., Freaney, R., Swan, M. 1970. Parathormone-like effect of magnesium replenishment in steatorrhea. *N. Engl. J. Med.* 282:61–68
80. Connor, T. B., Toskes, P., Mahaffey, J., Martin, L. G., Williams, J. B., Walser, M. 1972. Parathyroid function during chronic magnesium deficiency. *J. Hopkins Med. J.* 131:100–17
81. Woodward, J. C., Webster, P. D., Carr, A. A. 1972. Primary hypomagnesemia with secondary hypocalcemia, diarrhea and insensitivity to parathyroid hormone. *Dig. Dis.* 17:612
82. Levi, J., Massry, S. G., Coburn, J. W., Llach, F., Kleeman, C. R. 1974. Hypocalcemia in magnesium-depleted dogs: Evidence for reduced responsiveness to parathyroid hormone and relative failure of parathyroid gland function. *Metabolism* 23:323–35
83. Salet, J., Polonovski, C., DeGouyon, F., Pean, G., Melekian, B., Fournet, J. P., Aymard, P., Raynaud, C., Vincent, J. 1966. Tetanie hypocalcemique recidivante par hyomagnesemie congenitale: une maladie metabolique nouvelle. *Arch. Fr. Pediatr.* 23:749–68
84. Paunier, L., Radde, I. C., Kooh, S. W., Conen, P. E., Fraser, D. 1968. Primary hypomagnesemia with secondary hypo-

calcemia in an infant. *Pediatrics* 41:385–402
85. Stromme, J. H., Nesbakken, R., Normann, T., Skjorten, F., Skyberg, D., Johannessen, B. 1969. Familial hypomagnesemia. Biochemical, histological and hereditary aspects studied in two brothers. *Acta Paediatr. Scand.* 58:433–44
86. Anast, C. S., Mohs, J. M., Kaplan, S. L., Burns, T. W. 1972. Evidence for parathyroid failure in magnesium deficiency. *Science* 177:606–7
87. Suh, S. M., Tashjian, A. H. Jr., Matsuo, N., Parkinson, D. K., Fraser, D. 1973. Pathogenesis of hypocalcemia in primary hypomagnesemia: Normal end-organ responsiveness to parathyroid hormone, impaired parathyroid gland function. *J. Clin. Invest.* 52:153–60
88. Chase, L. R., Slatopolsky, E. 1974. Secretion and metabolic efficacy of parathyroid hormone in patients with severe hypomagnesemia. *J. Clin. Endocrinol. Metab.* 38:363–71
89. Targovnik, J. H., Rodman, J. S., Sherwood, L. M. 1971. Regulation of parathyroid hormone secretion in vitro: quantitative aspects of calcium and magnesium ion control. *Endocrinology* 88:1477–82
90. Buckle, R. H., Care, A. D., Cooper, C. W., Gitelman, H. J. 1968. The influence of plasma magnesium concentration on parathyroid hormone secretion. *J. Endocrinol.* 42:529–34
91. Sherwood, L. M. 1970. Magnesium ion and parathyroid function. *N. Engl. J. Med.* 282:752
92. Anast, C. S., Winnacker, J. L., Forte, L. R., Burns, T. W. 1976. Impaired release of parathyroid hormone in magnesium deficiency. *J. Clin. Endocrinol. Metab.* 42:707–17
93. Rude, R. K., Oldham, S. B., Singer, F. R. 1976. Functional hypoparathyroidism and parathyroid hormone end-organ resistance in human magnesium deficiency. *Clin. Endocrinol.* 5: In press
94. Hamilton, J. W., Spierto, F. W., MacGregor, R. R., Cohn, D. V. 1971. Studies on the biosynthesis in vitro of parathyroid hormone. II. The effect of calcium and magnesium on synthesis of parathyroid hormone isolated from bovine parathyroid tissue and incubation media. *J. Biol. Chem.* 246:3224–33
95. Neuman, W. S., Neuman, M. W. 1958. The chemical dynamics of bone mineral. *Univ. Chicago Rep.*, p. 55
96. MacManus, J., Heaton, F. W. 1970. The influence of magnesium on calcium release from bone in vitro. *Biochem. Biophys. Acta* 215:360–67
97. Pak, C. Y. C., Diller, E. C. 1969. Ionic interaction with bone mineral. V. Effect of magnesium, citrate, fluoride and sulfate on the solubility, dissolution and growth of bone mineral. *Calcif. Tissue Res.* 4:69–77
98. Au, W. Y. W., Raisz, L. G. 1967. Restoration of parathyroid responsiveness in vitamin D-deficient rats by parental calcium on dietary lactose. *J. Clin. Invest.* 46:1572–78
99. Jowsey, J. 1972. Calcium release from the skeleton of rachitic puppies. *J. Clin. Invest.* 51:9–15
100. Alcock, N., MacIntyre, I. 1961. Interrelation of calcium and magnesium absorption. *Clin. Sci.* 22:185–93
101. Kessner, D. M., Epstein, F. H. 1966. Effect of magnesium deficiency on gastrointestinal transfer of calcium. *Proc. Soc. Exp. Biol. Med.* 112:721–25
102. Lifshitz, F., Harrison, H. C., Harrison, H. E. 1967. Intestinal transport of calcium and phosphate in experimental magnesium deficiency. *Proc. Soc. Exp. Biol. Med.* 125:19–25
103. Morehead, R. M. Jr., Kessner, D. M. 1969. Effects of Mg deficiency and parathyroidectomy on gastrointestinal Ca transport in the rat. *Am. J. Physiol.* 217:1608–13
104. Dunn, M., Walser, M. 1966. Magnesium depletion in normal man. *Metabolism* 15:884–95
105. Radde, I. C., Wittermann, E. R., Pensuwan, S. 1968. Effect of thyroid and parathyroid on hypocalcemia occurring after a magnesium load. *Endocrinology* 83:1285–92
106. Care, A. D., Duncan, T., Webster, J. 1967. Thyrocalcitonin and its role in calcium homeostasis. *J. Endocrinol.* 37:155–67

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