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MAGNESIUM IN HEALTH AND DISEASE

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INTRODUCTION

Clinical magnesium depletion in humans was was first described in 1934 in a small number of patients with various underlying diseases (81). Flink and associates in the early 1950s documented depletion of this ion in alcoholics and in patients on magnesium-free intravenous solutions and described clinical consequences of this deficiency, often in association with depletion of other nutrients (59). A series of clinical case reports in the early 1960s helped focus attention on the occurrence of hypomagnesemia in various malabsorptive states and stimulated efforts to study magnesium depletion and its consequences under controlled conditions. Increasing numbers of clinical disorders associated with magnesium depletion have been recognized, including the effects of certain drugs that induce renal losses of this nutrient. Experimental and clinical observations have revealed fascinating interrelations of this ion with other electrolytes, second messengers, hormone receptors, parathyroid hormone secretion and action, vitamin D metabolism, bone function, and other changes associated with the fundamental roles of this ion in intermediary metabolism.

HOMEOSTATIC CONTROLS

Dietary Intake

Magnesium is widely distributed in foods. It is the mineral ion of chlorophyll; hence, green vegetables are an important source. Similarly, ingestion of animal products, legumes, and cereals helps assure a good intake. Intakes in a national survey in 1977–1978 of adult females and males averaged 230 and 310 mg, respectively (188a). These figures are very similar to those obtained with free-living healthy men and 18 women aged 20–53 years who subsisted on their customary diets and were analyzed periodically over a year. Their daily intakes varied greatly (e.g. from 132 to 350 mg for women with a mean of 234, and from 157 to 595 mg for males with a mean of 310 mg).

Absorption

Magnesium is absorbed primarily in the small intestine. Perfusion of the jejunum and ileum of normal human subjects indicated that both segments absorbed this ion equally well up to concentrations of about 10 mmol; the ileal absorption process became saturated above that concentration, while that in the jejunum increased (30). The usual enteric conditions with contraction or expansion of luminal volume tend to increase or decrease luminal magnesium concentration, with absorption being influenced significantly by water movement (i.e. solvent drag) (22).

Intestinal transport of magnesium in normal children was compared to that

in a child with the relatively rare genetically determined disorder called primary (or idiopathic) hypomagnesemia (134). Two separate transport systems appeared to participate in absorption from the proximal small intestine. One seemed to be a carrier-mediated system, which saturated at low intraluminal concentrations (2 and 4 meq/L); this system appeared to be defective in primary hypomagnesemia. The other system appeared to be that of simple diffusion and occurred at higher concentration (e.g. 20 meq/L).

Intestinal absorption data from earlier studies averaged from 50 (71) to 60–70% (128, 165, 190) on "usual" diets. More recent studies indicate a greater range (179). Free-living adults who had periodic evaluations over the course of a year while consuming self-selected diets had average absorptions of 21% for males and 27% for females (110). In various metabolic studies, the average absorption was appreciably higher but in most of these the diet was not self-selected.

VITAMIN D AND MAGNESIUM ABSORPTION In contrast to the demonstrated effect of the active metabolites of vitamin D on improving calcium and phosphate absorption in the intestine, the influence of this vitamin on magnesium absorption is uncertain. There are contradictory reports of no effect (82, 195) or of an effect (calcitriol at 2 μg per day) in the jejunum but not in the ileum (106). The latter study used segmental perfusion techniques and the data have been questioned (172).

Intestinal absorption of magnesium is reduced in a variety of malabsorption syndromes, in particular those associated with steatorrhea (Table 1). Chronic renal disease of varying severity has been reported either to reduce intestinal absorption of this ion to a major degree (30, 163, 177) or to have little or no effect (40, 105).

Renal Regulation

TUBULAR ABSORPTION Absorbed magnesium is retained either for tissue growth (including bone) or for use in turnover replacement; the unabsorbed remainder is excreted in the urine. Following glomerular filtration, tubular reabsorptive processes are key to magnesium homeostasis. As the result of micropuncture and in vitro microperfusion studies in the rat, rabbit, and dog, information has been gained on magnesium reabsorption along the nephron (149). Tubular secretion, if it actually occurs, must be a minor factor (149).

Eighty percent of serum magnesium in ultrafilterable, with 20 to 30% being absorbed in the proximal convoluted tubule (111, 149). The thick ascending limb of the loop of Henle appears to be the major site of magnesium reabsorption and the major site of control of excretion: 50–55% of filtered magnesium is resorbed between the thin descending limb and the early distal tubule (111, 149). Changes in concentration of magnesium in the tubular

Table 1 Clinical conditions associated with magnesium depletion[a]

Malabsorptive gastrointestinal disorders
Inflammatory bowel disease
Gluten enteropathy; sprue
Intestinal fistulas or bypass
Ileal dysfunction with steatorrhea
Immune diseases with villous atrophy
Short bowel syndrome
Radiation enteritis
Miscellaneous other disorders
Renal tubular dysfunction[b]
Metabolic
Hormonal
Drug-induced
Endocrine disorders[b]
Hyperaldosteronism
Hyperparathyroidism with hypercalcemia
Post-parathyroidectomy
Hyperthyroidism
Pediatric genetic and familial disorders
Primary idiopathic hypomagnesemia
Renal wasting syndromes[b]
Bartter's syndrome[b]
Infants born of diabetic or hyperparathyroid mothers
Transient neonatal hypomagnesemic hypocalcemia
Inadequate intake or provision of magnesium
Alcoholism
Protein-calorie malnutrition (usually with infection)
Prolonged infusion or ingestion of magnesium-low nutrient solutions or diets
Hypercatabolic states (burns, trauma), usually in association with previous entry
Excessive lactation

[a]Reproduced with modification from Ref. 172, pp. 164 and 165, with permission.
[b]See Table 2.

lumen and in the plasma affect renal absorption in this segment (151). The distal convoluted tubule was found to have a limited reabsorptive ability (< 5% of the filtered load) while the collecting tubules and ducts normally absorbed very little (35). Micropuncture studies have revealed that the urinary excretory pattern of this ion was a summation of the distinct transport properties of the proximal tubule and of the loop of Henle, so that a true maximum tubular reabsorption (Tm) was not operative (198).

METABOLIC AND DRUG INFLUENCES ON RENAL REGULATION Magnesium reabsorption in the nephron is influenced by a number of physiologic and metabolic factors as well as by drugs and disease states (Table 2). Of particular clinical significance with respect to renal losses are the loop diuretics such as furosamide and ethycrinic acid and certain nephrotoxic drugs. The diuretics triamterene and amiloride exert a magnesium-sparing effect, as they do for potassium (161). The renal tubular effects of cisplatin may develop rapidly with serious losses; furthermore, renal wasting may persist for many months after the drug is discontinued. A number of hormones affect magnesium absorption by the kidney (Table 2); for most the effects are usually small and may be indirect.

Summary of Homeostatic Factors

When magnesium intake is severely restricted in humas with normal kidney function on an otherwise adequate diet, output becomes very small (i.e. ≤ 0.5 meq/d) within 5 to 7 days (21, 169). Supplementing a normal intake increases urinary excretion without altering normal serum levels as long as renal function is normal and the amounts given are not excessive (76). The intestinal and renal conservation and excretory mechanisms in normal individuals permit homeostasis over a wide intake of dietary magnesium. Unlike sodium or calcium, there do not appear to be major hormonal homeostatic mechanisms for regulating serum magnesium. The normal range is the result of a balance between the gastrointestinal and renal absorption and excretion processes.

REQUIREMENTS FOR HEALTHY INDIVIDUALS

A large number of balance studies have been performed over the years in an effort to obtain quantitative data on magnesium requirements (reviewed in 110, 126, 165, 177, 178, 200). There is need for caution in accepting much of the older data because of analytic and procedural problems. Spencer et al (180) noted that 6 to 18 days are required for equilibrium to be established following changes in magnesium or calcium intakes. They note (179) that, of the 22 balance studies cited by Seelig (165), only four had been carried out longer than 15 days in any individual and only two had been performed in adults with a constant dietary intake in a hospital metabolic ward. Many of these studies were performed before accurate methods were available for determining magnesium in the presence of large amounts of calcium particularly, but also of phosphate in feces or in certain foods. The relative unreliability of older analytic data for magnesium in foods has been noted (188a). Atomic absorption spectrophotometry has been used widely since the

Table 2 Metabolic, hormonal, and drug influences on renal magnesium excretion[a]

Increased excretion (Ref.)
Hypermagnesemia[b]
Hypercalciuria (149, 151)
Hyperaldosteronism (88)
Hyperparathyroidism[c] (89)
Renal tubular dysfunction
Familial renal wasting syndromes
Primary magnesuric hypomagnesemia (78, 203); Bartter's and related syndromes (16, 20, 72, 73, 122)
Post-renal obstruction (43)
Post-renal transplantation (43)
Acute tubulointerstitial nephritis (29)
Nephrotoxic drugs
Amphotericin (31); cisplatin (23, 144)
Aminoglycosides (19, 101); cyclosporin (186)
Potassium depletion (143)
Alcoholism (57, 59)
Increased extracellular fluid volume (149)
Phosphate depletion (44, 107)
Diuresis
Diuretics (47, 86, 127, 149, 161)
Osmotic (diabetes, glucose, mannitol) (200)
Acidosis
Fasting (46); diabetic ketoacidosis (32); NH_4Cl administration (112)
Mineralocorticoids[d] (143, 148)
Hyperthyroidism (96)
Decreased excretion
Hypomagnesemia (21, 149, 169, 182)
Parathyroid hormone (89, 150)
Hypocalcemia (148)
Alkalosis (199)
Hypothyroidism (129)
Contracted extracellular fluid volume (149)
Antidiuretic hormone (167)
Calcitonin (148, 167)
Glucagon (17)
K^+,Mg^{2+}-sparing diuretics (161)

[a]Reproduced with modification from Ref. 172, pp 164 and 165, with permission.
[b]When associated with magnesium infusion/injection.
[c]Secondary to hypercalcemia; transient negative balance.
[d]Secondary to increased extracellular fluid volume.

late 1960s, with consequent improvement in ease and accuracy of magnesium determinations.

Balance studies have included observations on the possible influences of types of protein and amounts of proteins, fiber, calcium, and phosphate. The reports of effects on magnesium balances are often contradictory (110, 172, 177, 178, 180)

Serum magnesium levels were determined by atomic absorption spectrophotometry on a US population sample of 15,820 persons in the age range 1–74 years who were examined between 1971 and 1974 in the NHANES 1 survey (120). Ninety-five percent of adults aged 18–74 were in the range 1.50–1.91 meq/L. Younger individuals tended to have higher values. The levels of the fifth percentile were still at or above the lower levels of normal generally used in clinical laboratories (i.e. 1.40–1.45 meq/L). In this author's opinion, serum magnesium levels in healthy individuals are a good index of magnesium nutriture; hence, these data indicate that hypomagnesemia in the US population at that time was, and presumably still is, very uncommon from childhood to older age.

There is some question as to the reliability of the current RDA for magnesium, which are based on human milk content, consumption data, and older balance studies (60). They include 40 to 70 mg per day for infants, rising to 250 mg for children at 10 years. Recommendations for adolescent and adult males and for nonpregnant and nonlactating females fall in the range of 300 to 400 mg (5–6 mg/kg and 14–15 mg/100 kcal of recommended energy intake) with an additional 150 mg for pregnancy and lactation.

The currently "suppressed" 1985 report of The National Research Council–Food and Nutrition Board Committee on the RDA tentatively recommended that the RDA for magnesium be made "provisional"; most of the 1980 figures were retained with this proviso, but allowances for infants were reduced (i.e. to 30–50 mg/day and the additional amounts for pregnancy and lactation to 20 and 60 mg/day, respectively) (M. L. Brown, personal communication). A recent statement of the Food and Nutrition Board NRC/NAS posed these questions: "Since few studies have been devoted exclusively to magnesium requirements and the reliability of many of the resultant data is questionable, should there be an RDA or should only a provisional intake be established for magnesium?" and "Since there is no apparent evidence of magnesium deficiency in the general population, are data on the magnesium content of the average diet reliable enough to justify lowering the RDA?" (61). There is an obvious need for more quantitative data on the needs of various age groups using adequate analytic and more precise and prolonged balance techniques under strictly controlled conditions and, ideally, in conjunction with tissue biopsy analyses.

It is emphasized that the RDA are likely to be inadequate for those individuals with serious intestinal and renal absorptive defects and patients with serious hypercatabolic disease who are being nutritionally repleted. Analyses of serum levels, preferably with data on stool and urine magnesium losses, are needed to permit adequate replacement.

MAGNESIUM DEFICIENCY

Although the most studied, the rat is not representative of other species with respect to certain deficiency signs, e.g. the hyperemia, repetitive (and usually acutely fatal) tonic-clonic convulsions, and its peculiar serum calcium and parathyroid hormone changes. Mice on the same diet developed no hyperemia, became hypocalcemic, and often died with a single abrupt and massive convulsion (4). Deficient dogs and monkeys, also on diets of the same composition, developed spasticity, tremors, and occasionally nonfatal convulsions with hypocalcemia; increasing the oral calcium in the diet did not increase the serum calcium or prevent the neuromuscular changes (171).

Magnesium Deficiency in Humans

Symptomatic clinical human deficiency usually develops in a setting of predisposing and complicating disease states (Table 1) that often reduce intestinal absorption or are associated with impaired renal reabsorption (Table 2). Decreased intake or failure to provide adequate amounts of magnesium in parenteral or enteral preparations may be a complicating factor.

EXPERIMENTAL HUMAN STUDIES Four groups of investigators have recorded their efforts to induce magnesium deficiency experimentally in human volunteers (21, 40, 55, 169). In the one study in which symptomatic depletion occurred, the experimental diet provided about 0.8 meq of magnesium per day (169). Plasma magnesium fell progressively to levels that were 10–30% those of control periods. Erythrocyte magnesium declined more slowly and to a lesser degree. Urine and fecal magnesium decreased to extremely low levels within seven days. Hypomagnesemia, hypocalcemia, and hypokalemia were present in all of the consistently symptomatic patients. Good intestinal calcium absorption was associated with hypocalciuria so that the patients were in positive calcium balance. Serum phosphate values varied among the subjects. Most deficient subjects developed hypokalemia with negative potassium balance as the result of increased urinary losses. Serum sodium remained normal and the subjects were in positive sodium balance. Neuromuscular signs (positive Trousseau signs, tremors, fasciculations, and gross muscle spasm) occurred in five of the seven subjects after deficiency periods ranging from 25 to 110 days. Marked personality changes occurred in several patients.

All symptoms and signs (including personality changes) reverted to normal with reinstitution of magnesium. A characteristic finding (which has been repeatedly confirmed in cases of clinical magnesium depletion) was the delayed rise in serum calcium despite the rapid return to normal of serum magnesium upon magnesium repletion; a week or even longer intervened before calcium returned to baseline levels. Potassium balances became strongly positive as sodium balances became negative. The return of serum potassium to normal also required some days.

The signs and symptoms noted above in experimental deficiency have been described separately or in various combinations in clinical cases of hypomagnesemia. They included Trousseau and Chvostek signs, muscle fasciculations, tremor, muscle spasm, personality changes, anorexia, nausea, and vomiting. Frank tetany, myoclonic jerks, athetoid movements, convulsions, and coma have been reported. Convulsions with or without coma seem to occur much more frequently in acutely deficient infants than in adults.

CLINICAL DEFICIENCY The closest related condition to "pure" experimental human magnesium deficiency is an uncommon congenital primary hypomagnesemia occurring with a male:female ratio of about 2.5:1 (67, 182, 201) and related to a specific defect in intestinal absorption of this ion as mentioned above (27). Hypomagnesemia, hypomagnesuria, and hypocalcemia with tetany and often with convulsions were corrected with magnesium supplements. Calcium and vitamin D supplements were ineffective in maintaining normocalcemia. Serum potassium was low and sodium and phosphate elevated (182). During relatively short periods of depletion under controlled conditions in three subjects, serum immunoparathyroid hormone, calcitonin, and 25-OH vitamin D remained normal despite the hypomagnesemia (182).

ELECTROLYTE CHANGES IN BLOOD AND TISSUES Findings on serum/plasma calcium levels in various species from various laboratories have been summarized (170). In contrast to the rat, hypocalcemia occurred consistently in mice, dogs, monkeys, and human volunteers on the same magnesium-deficient diet providing 140 mg% of calcium (171).

Serum potassium In the two experimental human deficiency studies in which hypomagnesemia was observed, hypokalemia also occurred (48, 169). Teenagers with familial hypomagnesemia had low potassium levels (182). Hypokalemia has frequently been reported in adult clinical magnesium deficiency of various etiologies (59, 68, 98, 131, 191, 192) as well as in deficient malnourished children (15, 141).

Serum phosphate During experimental human depletion, the level of serum inorganic phosphate was variable, ranging from slightly elevated to low; following treatment with magnesium, three of the six patients had an abrupt fall in phosphate (169). Children with familial hypomagnesemia often have elevated serum phosphate; two of three such patients had a "spontaneous" fall in phosphate following repletion (182).

BONE METABOLISM A major proportion of magnesium in bone is complexed in the apatite crystal. Alfrey et al (6) noted that the surface-limited magnesium bone pool was rapidly utilized to replace other tissue deficits during deficiency. In contrast to muscle magnesium, that present in bone correlated well with serum magnesium in normal, depleted, and overloaded laboratory animals and human subjects (5).

Comparison of Human Experimental and Clinical Magnesium Depletion

THE VARIABILITY OF MAGNESIUM AND OTHER ELECTROLYTE CHANGES There are contradictory reports concerning the serum, muscle, and bone levels of magnesium in sick patients who were claimed to be magnesium deficient. The numbers of patients studied in most reports are small. The findings include (*a*) decreased serum and muscle magnesium with normal bone level (123); (*b*) decreased serum, variable muscle, and low bone magnesium levels (27); (*c*) normal serum and erythrocyte magnesium levels with decreased muscle magnesium and potassium (137); (*d*) reduced serum level with normal muscle content (140); (*e*) normal serum, erythrocyte, and bone magnesium levels with reduced muscle magnesium and variable muscle potassium (117); (*f*) consistently reduced serum concentrations with variable muscle levels (181); and (*g*) low serum magnesium with variable muscle magnesium concentration but with a highly significant correlation between serum and bone magnesium levels (5).

During magnesium deficiency, muscle magnesium may vary directly with muscle potassium in humans (5, 18, 59, 98). Conversely, the development of potassium depletion with depressed muscle potassium is associated with decreased muscle magnesium in humans (5, 7, 18, 98).

The bewildering variations noted in ill patients with respect to their blood and tissue magnesium and other electrolytes emphasize the difficulty in ascribing cause and effect to a specific nutrient deficiency in uncontrolled clinical situations. Normal cellular metabolism and the homeostasis of cellular components are critically dependent on an adequate supply of energy and the many essential nutrients. Significant deficiency of one or more can affect retention of other nutrients as noted above, e.g. magnesium deficiency depletes potassium while potassium depletion reduces the magnesium content of cells.

Starvation in obese subjects caused protein catabolism, acidosis and loss of cellular constituents including magnesium even though serum magnesium remained normal or nearly normal (46). Magnesium was lost from tissue by depletion of lean body mass and by an additional renal loss that appeared to be related, in good part, to the degree of acidosis. Muscle magnesium decreased; in addition the electrolyte excretion patterns indicated that very significant amounts came from bone. The serum magnesium was well maintained, presumably by a fairly constant input of magnesium into the blood from tissues.

This pattern of a normal or only slightly depressed serum magnesium despite major tissue losses undoubtedly occurs in illnesses where there is negative nitrogen balance with acidosis in patients who have depressed glomerular filtration either on a pre-renal (hypotension or hypovolemia) or on a renal basis. Such a situation could explain a number of case reports with the findings of normal or nearly normal serum levels despite depleted muscle levels. The same dichotomy between levels of serum and tissue magnesium could occur if potassium depletion rather than magnesium deficiency was the primary deficiency. These associated clinical complications would help explain the apparent contradiction between the consistent occurrence of progressive hypomagnesemia in experimental magnesium deficiency in humans and in experimental animals and those case reports in which the expected hallmarks of magnesium deficiency were not present. Such findings have led to the not uncommon claim that serum magnesium level is not a useful index of magnesium deficiency. In the complicated circumstances just noted this may be correct. However, diagnosis of magnesium depletion based on the magnesium concentration in a tissue or in separated cells, e.g. erythrocytes or white cells, may also be misleading because of the presence of other deficiencies that etiologically may be more important in affecting magnesium status. This author recommends that reports of cases believed to have magnesium deficiency should include sufficient clinical and biochemical data to permit better evaluation of whether the observed alterations (or lack of changes) in magnesium levels in tissue and serum reflect a primary or a secondary cause.

Physiological and Biochemical Correlates of Magnesium Depletion

The first reported magnesium-depleted patient with immunoparathyroid hormone assays had a genetically induced hypomagnesemia with undetectable immunoparathyroid hormone (12). Immunoparathyroid hormone levels rose markedly with magnesium administration and this was followed by a good calcemic response, which indicates that magnesium depletion was associated with a failure of the parathyroid gland either to manufacture or to secrete the

hormone. Over the next few years, as more cases with immunoparathyroid hormone measurements were reported, it became apparent that the relationships were more complex.

SEQUENCE OF THE EFFECTS OF MAGNESIUM DEFICIENCY AND REPLETION IN MAN

1. *Initiation of hypocalcemia* The initiating factor appears to be failure of the normal heterionic exchange of bone calcium for magnesium at the labile bone mineral surface (94, 145). Impairment of receptor responsiveness to parathyroid hormone of the osteoclasts then occurs with reduction of active bone resorption (64); hypocalcemia progresses despite increased levels of circulating parathyroid hormone (159).

2. *Perpetuation of electrolyte, parathyroid hormone, and clinical abnormalities* As depletion progresses, secretion of parathyroid hormone diminishes to very low levels despite adequate intraparathyroid gland hormonal reserves (13, 159). The hallmarks of severe magnesium depletion are present at this stage; namely, very low levels of circulating parathyroid hormone, unresponsive bone, hypocalcemia, hypocalciuria, hypokalemia, sodium retention, and neuromuscular and other clinical signs and symptoms (169).

3. *Regression of magnesium depletion and associated changes* With magnesium administration in adequate amount, serum magnesium rises. Magnesium ions enter the hydration shell of bone in increased amount, which permits heterionic calcium exchange to begin. This early exchange may explain the rapid improvement that occurs subjectively and some of the decrease in neuromuscular signs with little or no detectable change in circulating calcium. Depending on the amounts and intervals at which magnesium is given and its associated rise in serum (and presumably cellular magnesium), there is an increase in parathyroid hormone. With rapid infusion of relatively large amounts of magnesium, both the serum magnesium and hormone levels (particularly the latter) may be very high within a minute or so (13, 159). During this repletion interval, receptors to parathyroid hormone on the osteoclasts renew their responsiveness. As end-organ resistance recedes and parathyroid hormone levels remain elevated, serum calcium rises. With normalization of serum calcium, the hormone level declines appropriately. Electrolyte abnormalities recede, and clinical signs and symptoms disappear.

VITAMIN D LEVELS AND RESISTANCE IN MAGNESIUM DEFICIENCY Following original reports in rats (116), there have been a series of clinical cases suggesting that the calcemic effect of vitamin D—often in

high doses—is blunted in the presence of magnesium depletion in rickets (154), malabsorption (132, 146), and idiopathic (157) or surgically induced hypoparathyroidism (70). Parathyroid hormone is necessary for the formation of calcitriol (185) and calcitriol is necessary for parathyroid hormone to exert its effect on calcium mobilization from bone (66). A possible mechanism for vitamin D resistance is the lack of circulating parathyroid hormone in severe magnesium deficiency, with consequent depressed calcitriol synthesis. A patient who was surgically thyroparathyroidectomized and who became magnesium depleted was found to be resistant to calcitriol until repleted with magnesium, after which there was a good calcemic response (70). Circulating calcitriol has been variably reported to be decreased (65, 158), normal (152), or increased (93) in patients with magnesium deficiency. Despite low levels of calcitriol in the majority of reported cases, serum calcium rose after magnesium repletion (65, 158). Normal calcitriol levels are apparently unnecessary for the parathyroid-hormone-mediated response to magnesium. It also appears that resistance to vitamin D in magnesium deficiency, at least in the rat (36), is likely caused by impaired skeletal responsiveness to calcitriol. The cause in humans remains unknown.

CITRATE LEVELS As had been noted earlier in magnesium-deficient rats (24), patients who were either chronically depleted of magnesium as the result of intestinal malabsorption or acutely depleted by minimizing the magnesium content of their total parenteral nutrition solutions had a markedly decreased content of citrate in their urine. This was secondary to increased renal tubular citrate reabsorption (160).

MAGNESIUM DEPLETION IN VARIOUS DISEASE STATES

Prevalence

The list of causes of magnesium depletion (Table 1) emphasizes that this condition is likely to be found rather commonly in acutely or chronically ill patients. This is supported by various surveys. Of 2300 patients in a Veterans Administration hospital, 6.9% were hypomagnesemic (192); another study found 11% to have hypomagnesemia (196). The incidence of hypomagnesemia was investigated when other electrolytes were found to be below normal (192); hypomagnesemia occurred in 42% of patients with hypokalemia, 29% of those with hypophosphatemia, 23% of those with hyponatremia, and 22% of those with hypocalcemia. The distribution of the depressed values in the population was not given. In a retrospective study of 421 hospitalized patients in whom plasma magnesium and potassium had been measured concurrently, the incidence of hypokalemia was found to be 12%

while that of hypomagnesemia was 26% (28). Hypomagnesemia was present in 38% of the hypokalemic samples; hypomagnesemia was present in 25% of normokalemic samples. In 94 consecutive admissions to a medical intensive care unit, 65% of patients with a serum creatinine of $\leq$ 1.1 mg/dl were hypomagnesemic; of these, one third had hypocalcemia corrected with magnesium supplementation (162). In a study of 111 consecutive serum samples from hypocalcemic patients, 36 (32%) had serum magnesium $\leq$ 1.2 meq/L (103). These data suggest that magnesium determinations should be performed routinely on initial examination of acutely or chronically ill patients, especially those with poor food intake, malabsorption, hypokalemia, and/or hypocalcemia or those receiving diuretics or nephrotoxic agents.

Alcoholism

Magnesium depletion in acute and chronic alcoholism has been documented over many years. Causes include poor intake, increased urinary losses, vomiting, diarrhea, and ketosis (57, 59, 184). Thirty percent of all alcoholics and 86% of those with delirium tremens had hypomagnesemia during the first 24–48 hours after admission to a hospital (184).

Diabetes

Losses of magnesium in diabetic ketoacidosis have been appreciated for many years (32, 128). A significant negative correlation was noted between serum/plasma magnesium and blood glycohemoglobin in insulin-dependent pregnant women, with significant relationships to the rates of spontaneous abortion and malformation (136). Similar negative correlations were noted between serum (63) or plasma and muscle (173) magnesium and glycohemoglobin in insulin-dependent type I diabetics. Thirty-seven percent of infants born to diabetic mothers were found to be hypomagnesemic during the first three days of life; the degree of decline was related to the severity of maternal diabetes and prematurity (188). Children with insulin-dependent type 1 diabetes tended to have lower serum magnesium values than did nondiabetic controls (54, 63). Iron, copper, and zinc values were similar to those of controls (54). Serum magnesium levels increased significantly with improved diabetes control (63).

Malabsorption

Serum magnesium is often subnormal in patients with malabsorption syndromes of various etiologies (Table 1) (27, 124, 156, 168, 169). Increased amounts of fatty acids in the intestinal lumen form insoluble soaps with Mg^{2+}; this leads to loss from both dietary and endogenous sources. This well-established finding has been reconfirmed in malnourished adolescents with Crohn's disease given nutritional supplementation that further increased

the fecal magnesium level but not the levels of nitrogen and calcium (139). Restriction of fat can play a role in managing magnesium-losing steatorrhea (27).

Protein-Energy Malnutrition

Magnesium depletion occurs in children with inadequate intake in association with malabsorption, persistent vomiting and/or diarrhea, and infection. Serum or plasma magnesium was noted to be low in various studies in Africa, i.e. in 19 of 28 children (33), in 39 of 100 (156), and in 10 of 13 having serum values below the lower limit of normal and all having very low urinary magnesium (119). In a study in Central America 50% of serum magnesium values were below 1.3 meq/L on admission to treatment and during recovery in unsupplemented children, and an equal percentage had low muscle magnesium (141). Some children had elevated serum and muscle magnesium; it was speculated that these were related to reduced renal function, which was known to occur.

Kidney Disease and Nephrotoxic Drugs

A number of factors may modify adversely the critical role of the kidney in magnesium homeostasis (Table 2). When impaired glomerular filtration or tubular obstruction are significant, hypermagnesemia is usual. Nevertheless, magnesium depletion can occur in chronic renal failure because of concomitant poor intake and muscle wasting or losses associated with vomiting, diarrhea, malabsorption, diuretics, nephrotoxic drugs, acidosis, and/or use of magnesium-free dialysate (102, 118, 133, 135, 147). Increased excretion is associated with postobstructive nephropathy, chronic glomerulonephritis, acute tubulointerstitial nephritis, post renal transplantation, and familial urinary magnesium-wasting syndromes (78, 203). While hypomagnesemia may occur, it is not a common finding in Bartter's syndrome (20) or a related syndrome (72, 73); however, there is a sparing effect of magnesium on renal losses of potassium (16, 72, 73, 122).

Some drugs of importance in clinical practice may significantly impair renal conservation of magnesium (Table 2). Cisplatin is of particular concern in that it affects a large proportion (144) or all (23) of recipients to the point of hypomagnesemia caused by renal wasting. The tubular defect may occur shortly after initiating the drug and may persist for months or even years after its discontinuation.

The risk of stone formation and nephrocalcinosis in magnesium-depleted rats is well documented. It is quite possible that long-term unrecognized chronic magnesium depletion in humans with a good calcium intake could lead to soft tissue calcification. There is a more frequent risk associated with the hypocitraturia that occurs within a matter of days in magnesium-depleted

patients (160). Since both citrate and magnesium tend to keep calcium from precipitating in urine, the value of maintaining adequate urine concentrations of both is obvious.

Post-Parathyroidectomy Hypomagnesemia

Cases have been described of symptomatic hypomagnesemia following parathyroidectomy for primary hyperparathyroidism in association with the expected hypocalcemia. Symptoms of muscle weakness, tremor, and mental changes were reversed by magnesium repletion despite continuing low calcium levels (e.g. 97). This appears to be a manifestation of the "hungry bone" syndrome following removal of the parathyroid adenoma in which not only calcium but also magnesium are deposited into bone at a rate exceeding absorption.

Antiepileptic Drugs

Earlier claims have been made that serum magnesium levels are lower than controls in epileptic patients treated with antiepileptic medications (38). More recent evidence, however, indicates that epileptic patients on such drugs, e.g. diphenylhydantoin (202) with or without phenothiazines, had serum (202) or cerebrospinal fluid (79) magnesium levels similar to those of matched untreated controls.

MAGNESIUM ALTERATIONS AND POSSIBLE DISEASE DEVELOPMENT

Cardiac Abnormalities

CORONARY ARTERY DISEASE It has been suggested that there is an inverse relation between magnesium intake and coronary artery disease and its sequelae (9, 128, 166). The prevalence, morbidity, and mortality of this disease are such that these claims merit brief examination here.

Role of water hardness Some epidemiologic reports have noted decreased prevalence of deaths from coronary artery disease in areas where the water is "hard" (i.e. higher in calcium, magnesium, and fluoride than is "soft" water) (14, 41, 121). Marier (126) has summarized data on the contents and ratios of calcium and magnesium and has noted the wide variations encountered. It was noted in a relatively small case control study that "very low fluoride and perhaps magnesium intakes are associated with an increased risk of atherosclerosis"; however, the variability of intake was so great among cases of myocardial infarction and controls that the mean intakes were not significantly different (121). A study in England and Wales found no association between the myocardial concentration of magnesium or calcium and their

levels in domestic tap water (53). Hammer & Heyden (74) summarized briefly a series of studies that failed to implicate a causal relation between water hardness and heart disease, particularly cardiovascular disease mortality. More recently, Leoni et al (113) recorded negative correlations for cardiovascular diseases and water hardness in 11 Italian locales during the period 1968–1978. Hence, there is no consensus regarding the role of hard water as a factor in modifying coronary artery disease prevalence.

Magnesium intake and myocardial mortality The intake of magnesium in the US is stated to have declined from earlier in the century (188a); at the same time there has been a major decline in age-adjusted death rate from ischemic heart disease in the US (75). These data imply that a modest decrease in the level of intake of magnesium is not likely to play a causative role in the manifestation of this disease.

Serum values of magnesium in acute myocardial infarction The data in older reports are conflicting, but the majority noted that the patients had decreased serum or plasma values "soon after" or "upon admission" to the hospital. More recent data cast doubt on this claim and emphasize that the time of drawing blood is critical. Magnesium values in the patients with acute myocardial infarction on day 1 were significantly less than controls (1, 49, 125, 153) but only when there were complications (with a return to normal by day 3) (153) or severe coronary artery disease detected by angiography (125). Patients in a coronary care unit with or without infarction had similar magnesium values (49). Following coronary artery surgery, there was a similar and significant decline postoperatively in the levels of serum magnesium in those patients suffering acute infarction and in those without infarction (62).

Speich et al (176) noted that in intensive care unit patients with acute myocardial infarction, plasma magnesium rose significantly by the third day; erythrocyte magnesium rose more slowly, as did plasma and erythrocyte zinc. The initial plasma values obtained within three hours of pain onset in the infarcted males were not significantly different from those of control males. There were significant positive correlations between plasma or erythrocyte magnesium and creatine kinase isoenzyme MB as an indicator of infarct size; this suggested that magnesium left the heart at the time of the infarction and entered the extracellular compartment in proportion to cardiac enzyme activities (174). Data from patients with unstable angina on admission suggested that hypoxia without significant necrosis also caused magnesium to leave cardiac muscle (174). This is consistent with a prior finding of a larger decrease in myocardial magnesium in men with a prior history of angina who died suddenly of heart disease as compared to those without prior angina (95).

In only two of these reports (49, 125) was there any mention of medications

being used by the patients prior to the studies. The serum magnesium levels were significantly lower in the patients on either digitalis drugs or diuretics (125). A significant proportion of coronary care unit patients with or without infarction were on either digitalis or diuretic drugs (49).

Lipolysis occurs soon after the onset of symptoms of acute myocardial infarction; similar changes have been noted with ethanol withdrawal, epinephrine administration, surgery, cold stress, and severe exercise (58). Flink et al (58) found a mean rise of free fatty acids to about three times baseline in 16 patients shortly after infarction, and this was associated with a decrease in magnesium level of 0.22 meq/L (58). The rapid fall in free fatty acids in the ensuing 48–72 hours was associated with a rise in serum magnesium to normal levels in 48 hours. It was suggested that free fatty acids bind magnesium ions; this binding may result in decreased free Mg^{2+} concentration, especially in patients depleted of magnesium by poor intake or diuretic treatments.

No association has been noted between the levels of serum magnesium and the presence or absence of clinically apparent chronic coronary artery disease (3). On the other hand, there is some reduction—small but significant—in noncardiac patients with painful conditions requiring acute surgery or in medical patients with painful noncardiac diseases or in women in labor. Patients with surgical, medical, or obstetrical conditions without pain had normal magnesium levels (2).

Magnesium content of the myocardium There are a moderate number of reports from 1950 to 1980 reporting decreased magnesium in the myocardium of patients dying with ischemic heart disease (cf 126, 166). More recent data indicate the complexity of magnesium distribution in the heart (175). In human hearts obtained at necropsy, the left ventricle from individuals without infarction who died following acute trauma had approximately 11% more magnesium than in the right ventricle. These subjects served as controls. Both ventricles (noninfarcted areas) from patients dying of acute myocardial infarction had 20–28% less magnesium than in the control ventricles; magnesium in the infarcted areas of left ventricles was only one half that in controls. Potassium, calcium, and sodium concentrations were also lower in the noninfarcted portions of the heart compared to those of controls. As the result of cytolysis and anoxia in the infarcted areas, the Mg/Ca ratios were significantly inverted and the K/Na ratios very significantly smaller. No data was given about the medication history of the patients with infarction.

The cause(s) and significance of the decreased magnesium content in ischemic hearts are not clear since there are many complicating factors and such information is not included in most of the published reports. These complicating factors include duration of the heart disease, prior medications

and dietary therapies, elapsed time between the infarction, death and tissue sampling, areas of sampling, and variability in sampling. What the reported changes in magnesium content have to do with the state of magnesium nutrition (if anything) is uncertain.

CARDIAC ARRHYTHMIAS AND SPASMS There has been increasing attention to the relationships of depletion of magnesium and other electrolytes, particularly potassium, as factors contributing to the development of coronary artery spasm and of various arrythmias and associated increased cardiac morbidity and mortality. Salts of magnesium have been used empirically on occasion for some 50 years in the treatment of various tachyarrythmias occurring with ischemia, digitalis toxicity, and diuretic therapy (52a). In 1966 it was found that magnesium-deficient monkeys and dogs had increased susceptibility to serious arrythmias when given acetylstrophanthidin (104). The relation of hypokalemia and clinical arrhythmias has been known since 1949 (80). Increasing understanding of the close physiologic, biochemical, and clinical interrelations of magnesium and potassium as well as of calcium and sodium have made it apparent that either magnesium or potassium depletion can influence the serum and cellular concentrations of the other and that certain drugs can adversely affect serum and tissue concentration of each. The frequency of hypokalemia and hypomagnesemia in hospitalized patients has been noted earlier.

The rationale for intervention has been based on physiologic considerations of changes in electrolyte concentrations (including magnesium); of membrane interactions involving potassium, magnesium, sodium, and calcium; and of calcium-magnesium antagonism (92, 115). It has been postulated that the beneficial effects of magnesium reside in its action as a calcium blocker and that magnesium depletion leads to loss of cellular potassium and to an increase in calcium, failure of membrane Ca-ATPase to extrude calcium from the cell, and influx of calcium into mitochondria (92). Recent evidence indicates that addition of Mg^{2+} in physiologic amounts to isolated ventricular (189) or atrial (87) cells very rapidly blocks K^+ channels, which causes inward rectification. This role of Mg^{2+} ensures a low conductance of cell membranes at the plateau of action potentials during exposure to acetylcholine, which thereby slows heart rate without unfavorable shortening of the action potential.

Hypokalemia in patients with acute myocardial infarction is associated with increased risk of ventricular arrhythmias (99, 142). Hypokalemia was noted in 17% of patients, whereas hypomagnesemia occurred in 6%. Ventricular arrhythmias occurred in 10 of 13 patients with infarction who were hypomagnesemic; 8 of these were also hypokalemic. Patients with infarction were twice as likely to be hypokalemic on admission (22 vs 10%) if they had been

on prior diuretics. The occurrence of serious arrhythmias was more common in those with hypokalemia. Mean plasma concentrations of both potassium and magnesium were lower in diuretic-treated patients than in a nontreated control group (28). Hypomagnesemia was identified in a significant percentage of hypokalemic patients (52). The incidence of serious ventricular ectopic beats, ventricular tachycardia, and ventricular fibrillation on admission of patients to the coronary care unit was higher in hypomagnesemic patients with acute myocardial infarction, as was atrial fibrillation and supraventricular tachycardia. On the other hand, atrioventricular block and supraventricular bradycardia were higher in the hypermagnesemic patients (49). In a series of 136 serum samples sent to the laboratory for digitalis estimation, hyponatremia was found in 21%, hypomagnesemia in 19%, and hypokalemia in 9% (193).

Hollifield (86) measured serum potassium and magnesium in patients with mild to moderate hypertension given increasing amounts of hydrochlorothiazide up to 50 mg/day. The levels of both ions were lower than those of controls but were within normal levels; both decreased progressively to subnormal levels at 100 mg/day and higher (86). Exercise was associated with premature ventricular contractions in patients on hydrochlorothiazide; this correlated highly with decreased serum potassium and magnesium. Clinically stable hypertensives eating well on long-term and usual doses of thiazide diuretics (50 mg/day or less) had only slightly lower serum magnesium levels on the average than controls, and low levels were rare (109).

An increase in sudden death was noted in the Multiple Risk Factor Intervention Trial in a subgroup of patients with baseline electrocardiographic abnormalities who were part of the special intervention group of hypertensives who received a higher dose of diuretics and developed a greater degree of hypokalemia. The hypokalemia was not uniformly corrected at the time the study was initiated since it was not believed to lead to ventricular ectopic activity in hypertensive patients without overt cardiac disease (168). More recent studies provided evidence that such a view was not correct (34, 83, 90).

A series of recent symposia have been concerned with electrolyte changes and cardiovascular mobidity and mortality (26, 84, 85). Since hypokalemia and hypomagnesemia can be induced by the same mechanisms and are often clinically correlated with one another, magnesium as well as potassium should be routinely measured in situations, such as diuretic therapy, where they may occur (194). Electrolyte balance should be maintained by either supplementation or more appropriately by the choice of diuretic agents in patients with cardiac disorders that do not induce hypokalemia and hypomagnesemia (e.g. combining thiazides with triamterene or amiloride.

Should magnesium therapy be given to eumagnesemic patients with ar-

rhythmias? Several short-term studies (12–18 hours) suggest a decrease in arrhythmias with such therapy (50, 91).

Coronary artery tone In recent years interest and concern have been stimulated by reports of increased coronary artery tone in vitro (i.e. "spasms") in magnesium-depleted solutions and by the hypothesis of a possible relationship to sudden death in ischemic heart disease (10). A reciprocal relationship has been suggested between calcium and magnesium ions in the modulation of vascular smooth muscle reactivity (8). Others have found that the concentration of Mg^{2+} in the in vitro bath must be very low to induce even a moderate increase in smooth muscle tone (100); the dilator effect of an 8-fold increase in cerebrospinal fluid magnesium (1.2 to 9.6 meq/liter) was modest (164).

Recent data on the relationship of magnesium depletion in the bath fluid of isolated coronary artery rings emphasize the complexity of the role of magnesium and its intimate relationship with other ions. An endothelium-dependent relaxation was reported to require magnesium ions, i.e. lack of magnesium was associated with constriction upon exposure to acetylcholine (11). Using a similar technique, others have found that omission of magnesium produced a potent *vasorelaxant* response when the arterial endothelium was intact but a *vasoconstriction* when the endothelium was disrupted (108). The relaxation associated with omission of magnesium was completely abolished by lowering the extracellular calcium levels, presumably by inhibition of the Na^+/Ca^{2+} exchange mechanism in endothelial cells. The vasoconstriction, on the other hand, appears to be related to a reciprocal increase in calcium influx into smooth muscle cells, possibly via the calcium slow channel (108). In both these studies, magnesium was either present or absent from the bath so that no data are available on minimum concentrations required for normal responses. The relation of these observations to the reactions of intact and damaged human coronary arteries to decreased magnesium is unknown.

Magnesium in cardioplegic solutions Cardioplegic solutions are designed to induce rapid diastolic ischemic arrest, minimize the extent of ischemic injury, and prevent myocardial damage during reperfusion after aortocoronary bypass. A high magnesium content in cardioplegic potassium solutions was effective with rat hearts but not with rabbit hearts and perhaps not with other species (25). In a prospective randomized study of 76 patients undergoing coronary bypass grafting with varying concentrations of magnesium (zero or 0.25 meq/L) in the solution during bypass with the aorta clamped or with 0.375 meq/L before bypass, magnesium administration did not affect resumption of a cardiac rhythm or spontaneous defibrillation during reperfusion (77). The number of shocks to initial and to sustained defibrillation and the energy required for the last direct-current shock were greatest in the patients who

received magnesium before bypass and in those whose plasma magnesium was greater than 2.26 mg/dl (1.88 meq/L).

Hypertension

Older studies have noted lower mean serum magnesium levels in hypertensives as compared to normals (e.g. 1.4 vs 1.6 meq/L) (3a) or lower values in hypertensive men but not women (21a). In an intervention study, hypertensive patients on diuretic therapy were given 365 mg of magnesium as the aspartate-HCl. They showed a subsequent drop in blood pressure over six months with no change in plasma magnesium or other electrolytes (51). In a limited number of reports on magnesium intake in relation to the presence of hypertension, one indicated no difference from normotensives (187) and another lower intake by hypertensives (130).

Serum ionized calcium, total magnesium, and plasma renin activity were determined in 102 normotensive patients and 98 patients with essential hypertension (off medications for at least two weeks) and with essentially normal serum urea nitrogen and creatinine values (155). Patients with low-renin hypertension had serum magnesium levels of 2.07 ± 0.03 meq/L, those with normal renin had 1.94 ± 0.02 meq/L, and those with high renin had 1.83 ± .02 meq/L. Each group was significantly different fron the others, and the high- and low-renin groups differed significantly from the normotensive group, which had a magnesium value of 1.91 ± meq/L. Opposite relations were noted for serum ionized calcium in these patients. The range of variability within all groups covered essentially the normal clinical range. The physiologic and biochemical relevance of these relatively small but apparently statistically significant changes is still unclear but may be related to changes in intracellular Ca^{2+}, which could act by affecting renin, parathyroid hormone secretion, and vascular tone. The importance of monitoring serum magnesium and potassium in hypertensive patients on electrolyte-wasting diuretics has been emphasized.

MAGNESIUM REPLETION

The physician should anticipate hypomagnesemia in relevant clinical situations and institute therapeutic regimens to prevent its occurrence. Such preventive measures include (*a*) treating underlying disease, (*b*) minimizing therapeutic insult, and (*c*) initiating nutritional and dietary intervention to improve intake and to decrease magnesium losses in stool and urine.

When the patient presents for the first time with hypomagnesemia, the etiology should be determined. If the cause is uncertain, measurement on the same day of serum and urine magnesium levels is indicated. If the serum magnesium is consistently subnormal (i.e. < 1.2 meq/L), the normal kidney

will excrete only small amounts of magnesium (i.e. < 2 meq per day). If renal tubular insufficiency is present, urinary magnesium will be appreciably higher—to the point where it may equal or exceed the magnesium absorbed from the intestine or that given parenterally.

The amount and route of magnesium administration depends upon the severity of depletion, its etiology, and intestinal and kidney functions. Symptomatic deficiency is best treated by the intravenous or intramuscular route in conjunction with any indicated therapy for the underlying condition and with correction of other electrolyte and acid-base abnormalities. Initiate treatment in symptomatic adolescents and adults with good renal function with 3 g (25 meq) of 50% magnesium sulfate given intravenously over 2 or 3 hours in saline or dextrose solutions with other nutrients as required. Another 3–4 g are then given by continuous infusion over the remaining 24 hours or by periodic intramuscular injections. This administration is given daily for several more days and the situation reassessed. For the asymptomatic patient with very low serum levels (i.e. ≤ 0.06–0.8 meq/L) the dosage prescribed above is indicated; when the serum level is higher, half the dosage parenterally or orally should be sufficient unless renal losses are very high.

Intravenous calcium administration in the treatment of the secondary hypocalcemia is usually unnecessary unless overt or latent tetany is apparent.

The return of serum magnesium to the normal range is relatively rapid. Repletion of magnesium lost from bone and other tissues requires a more prolonged period of magnesium therapy; the need is evaluated by periodic serum and/or urine magensium levels as the magnesium dosage is progressively reduced.

Where indicated and feasible, supplementary magnesium may be given as tablets of milk of magnesia (MgO) or as gelatin capsules packed with powdered magnesium sulfate (Epsom salts), magnesium chloride, or magnesium oxide. One tablet or capsule is given 3 to 6 times per day. Improvement of existing steatorrhea will decrease fecal magnesium losses.

The need for prolonged magnesium therapy that cannot be met adequately by increased oral intake presents a practical problem. Intramuscular injection of magnesium salts is painful and when given chronically often induces a fibrotic reaction. The alternative is intravenous infusion or the old-fashioned but useful hypodermic clysis. In the latter procedure a dilute solution of 50% magnesium sulfate (e.g. 2–3g in 150 ml of 0.45% saline) is infused slowly over 3 to 4 hours through a small needle inserted under the skin over the abdomen as frequently as is necessary. The intravenous route may be through a peripheral line, percutaneous catheter into the subclavian vein, or for very prolonged infusion, via a tunneled central venous catheter. The daily requirement for magnesium (and any other electrolytes that are needed) may be given intravenously in a matter of 3 to 4 hours daily or less frequently at home.

Alternative programs of magnesium replacement in deficient adults have been utilized, usually with higher doses than advocated here. Flink (56), for example, has recommended 112 to 128 meq intramuscularly or intravenously over the first day, with smaller doses subsequently.

Experience in the treatment of symptomatic magnesium depletion in infants repeatedly confirms the rapid efficacy of relatively small amounts of intravenous or intramuscular magnesium in controlling neurologic signs and restoring serum levels (39, 197). Parenteral administration is recommended at 0.3–0.5 meq (3.6–6 mg) per kilogram body weight as 50% magnesium sulfate over the first several hours, followed by an equal amount either intramuscularly or intravenously over the remainder of the day. If the child is symptomatic, calcium should also be infused with potassium and other electrolytes as indicated. Duration, route of administration, and dosage will depend upon the severity and etiology of the depletion. Where chronic malabsorption is marked, as in primary magnesium depletion, 1.0–1.5 meq/kg orally in multiple divided doses should be tested; experience has indicated that this dosage schedule raises serum levels to nearly normal without inducing diarrhea (182).

HYPERMAGNESEMIA AND MAGNESIUM TOXICITY

Magnesium salts as cathartics have a long history and are still in use, with the sulfate, hydroxide, and citrate forms being commonly used. Since 20% or more of Mg^{2+} may be absorbed and may have a systemic effect in the presence of renal insufficiency, magnesium salts are best avoided in such patients.

The normal kidney is capable of excreting absorbed or injected magnesium ion so rapidly that serum levels do not rise to clinically dangerous levels. In the treatment of preeclampsia, eclampsia, and premature labor with magnesium salts, relatively massive doses have been given as a loading dose followed by maintenance doses; the objective is to maintain the serum level at 5 to 8 meq/L (37, 42, 45). Patients with normal kidneys were able to excrete 40–60g of magnesium sulfate per day when given by persistent infusion (56). Hypermagnesemia may develop in other clinical situations in which magnesium-containing drugs, usually antacids or cathertics, are given to individuals with renal insufficiency or when large amounts of the ion are given inadvertently by the parenteral routes (138). In acute renal failure with oliguria, especially in the presence of acidosis, tissue release in association with the usual intake of magnesium results in some degree of hypermagnesemia.

Mordes & Wacker (138) reviewed in detail the effects of magnesium excess, which are multiple and potentially lethal, especially above 8 meq/L.

Uremic symptoms may mask those of hypermagnesemia. The widely held belief that magnesium is an anesthetic and a major central nervous system depressant is not correct unless it is given intrathecally or intraventricularly or is applied directly to nervous tissue (138). Uptake of magnesium from the blood into the central nervous system is quite limited. Calcium infusion counteracts magnesium toxicity, but dialysis is the treatment of choice (86).

Serum magnesium levels should be obtained in all instances of acute renal failure at suitable intervals and monitored in chronic renal insufficiency. Hypermagnesemia should be suspected in instances of low anion gap in stable patients and of normal anion gap in severely ill acidotic patients (86).

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