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Excess Magnesium

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I. Introduction

The importance of magnesium (Mg) in biological processes has gained increasing attention as reliable methods for its measurement have become available (440). In particular, states of Mg depletion have been the subject of intensive investigation and review (278, 358, 440). States of Mg excess, however, have not been as extensively reviewed. In view of an increasing volume of experimental data, the persistent appearance of reports of Mg intoxication (17, 61, 136, 143, 161, 217, 261, 313, 328, 335, 350, 357, 429, 434) and the continuing use of Mg as a therapeutic agent, review of the effects of excess Mg would appear to be of use to both clinicians and investigators.

Excellent general reviews of Mg metabolism are those of Walser (449), Bacq (29), Wacker and colleagues (440, 442), and Aikawa (8), whose monograph incorporates material pertinent to veterinary medicine. The biochemistry of Mg is reviewed by Wacker (439) and will not be considered in detail here. Walser (449) lists reviews available in the European literature; many older reviews in English are of historical interest (124, 188, 444).

II. Magnesium Homeostasis

Total body stores of Mg are on the order of 2000 mEq (458) of which about one-half reside in bone (8). Among nonosseous tissues, liver and striated muscle have the highest Mg concentrations, between 15 and 20 mEq/kg (7). The normal serum Mg concentration ranges between 1.5 and 2.5 mEq/liter (466). About one-third of plasma Mg is protein bound (282, 386); the major part of the remaining diffusible fraction is free ionized Mg (449). Regulation within these limits is precise (440), and routine serum Mg analysis as a screening procedure uncovers few abnormalities (216). Normal cerebrospinal fluid Mg is 2.0 to 2.4 mEq/liter (255). Normal erythrocyte Mg ranges from 4.4 to 6.0 mEq/liter but may increase in the presence of elevated serum Mg (394, 446).

It should be pointed out that, unlike calcium, the serum magnesium concentration is not maintained between narrow limits by a complex system which, in the case of calcium, includes parathyroid hormone, calcitonin, and vitamin D. Inasmuch as the concentration of *ionized* calcium is critical to many important biological functions including nerve conduction, muscle contraction, and secretion, it has been important, in evolutionary terms, to develop the finely tuned regulation of the extracellular concentration of this ion. In the case of Mg, the serum concentration is less critical and will fall in the presence of a deficiency of the element.

Positive Mg balance is maintained on an intake of 0.35 mEq/kg of body weight per day (221), and the typical American diet contains about 25 mEq/day (120, 440). There appear to be no foods uniquely high in Mg content (452). Higher daily intake, up to 82 mEq (1 gm)/day, has been advocated as a therapeutic measure (420), but high oral intake of Mg may cause substantial phosphate depletion (267) as well as small alterations of calcium (Ca) and nitro-

gen balance (191). Hypokalemia and acidosis have been reported with massive ingestion of magnesium oxide (434). Over one-half an oral Mg load is excreted in feces (10), although the fraction varies according to the dietary abundance of Mg (34, 164). Absorption of the remaining fraction occurs in the small bowel (6, 78, 164) and is to a variable extent influenced by large doses of vitamin D (177), antibiotics (192), protein (293), and dietary phosphate and Ca (12, 39, 78). Absorption of Mg from antacids and purgatives has been documented (120, 357, 453, 456). The precise locus and mechanism of transport remain subject to controversy (63). Calcitonin may play a role in the regulation of postprandial serum Mg levels (33), but its mechanism of action is unclear.

The major excretory pathway for Mg is renal, and both oral and intravenous loads are rapidly eliminated (30, 84, 191, 352). Only 1 to 2% of an intravenous Mg load is recoverable in feces (440). Regulation of excretion in humans is determined by both filtration and reabsorption with approximately 1800 mg of Mg being filtered into the glomeruli daily, but only 3 to 5% of that Mg is lost in the urine (289). Most reabsorption occurs isotonically in the proximal tubule (68) and exhibits a T_m. The reabsorptive mechanism is believed to work at or near saturation (30, 84), although in the Mg-deficient state, renal conservation is pronounced (34, 137, 294). Massry *et al.* found the T_m for Mg in the dog to be 140 μg/min/kg of body weight (287); Knippers and Hehl (241) found Mg reabsorption to be maximal when serum Mg was about four times normal. The data regarding possible tubular secretion of Mg are conflicting (15, 27, 67, 68, 157, 287, 455). Available data do indicate, however, that if Mg excretion does exist, its role in Mg handling is minor; the issue is reviewed by Massry and Coburn (284). Parathyroid hormone in the absence of hypercalcemia increases the tubular reabsorption of Mg (268, 284, 287). Hypercalcemia increases Mg excretion (94, 285) and probably accounts for the normal or low Mg levels seen in hyperparathyroidism (284). The effects of calcitonin on Mg are variable and may be species-specific. Decreased urinary excretion is reported in rats (13, 346) and sheep (32). Both decreased excretion (102) and no effect (89) have been reported in the dog. In man, both no change (96) and an increase in Mg excretion (332, 387) have been observed. As Mg loads are excreted, increased amounts of sodium, chloride, and Ca are also excreted (84, 231, 241). Hyperaldosteronism has been observed to increase the clearance of Mg without affecting serum Mg (195, 208). The renal handling of Mg is also affected by vitamin D, growth hormone, thyroid hormone, and a number of other factors which are reviewed by Massry (282, 284). The exact mechanisms by which magnesium homeostasis is so precisely maintained remain only partly understoood.

III. Hypermagnesemic States

A. Introduction

It is well recognized that impaired renal function is the most common prerequisite for the development of hypermagnesemia (440). The other common associated finding is the use of Mg-containing medications. Symptomatic hypermagnesemia is often an iatrogenic disorder. In addition to use in purgation, antacid therapy, and replacement in recognized deficiency states, Mg has found advocates in a wide variety of disorders, including neonatal tetany (433, 469), hyperuricemia and hyperlipidemia (140), lithium toxicity (464), hyperthyroidism (180, 211, 322), pancreatitis (206), hepatitis (422), phlebitis, coronary artery disease (420), arrhythmia (76, 98, 266), and digitalis intoxication (321, 380, 381, 388, 406, 419). The clinical settings of hypermagnesemia are summarized in Table 1.

B. Increased Absorption Due to Excessive Intake

Hypermagnesemia following *oral* ingestion in the absence of either intestinal or

TABLE 1
Clinical settings of hypermagnesemia

Common:	Acute renal failure
	Chronic renal failure with exogenous Mg intake
	Toxemia therapy
Less Common:	Chronic renal failure without exogenous intake
	Rectal administration of Mg-containing solutions (131, 328, 359, 410)
Uncommon or Producing Only Small Elevations of Mg:	Parasitosis with exogenous Mg intake (73)
	Lithium therapy (297)
	Hypothyroidism (178, 220, 446)
	Certain neoplasms with skeletal involvement (269)
	Viral hepatitis (82)
	Hyperparathyroidism with renal disease (178)
	Pituitary dwarfism (178)
	Milk-alkali syndrome (178)
	Perforated viscus with exogenous Mg intake (292, 313)
	Acute diabetic ketoacidosis (279)
	Addison's disease (197, 442)

renal disease has not been documented, but may have occurred in one apparently well male following massive overdosage (335). Increased absorption of excess Mg may occur in parasitosis (73), but not in the case of experimental anoxic bowel preparations (436). *Rectally* administered Mg has been shown to cause hypermagnesemia in the absence of renal failure in animals (23, 253), in adults (131, 359, 410), and in the neonate (328). This last observation is of importance in light of the advocacy of the osmotic properties of Mg as therapy in hyaline membrane disease (414) and remains a subject of some contention (415). Fatal hypermagnesemia from rectal administration has been reported in cases of megacolon (97) and bowel obstruction (56).

C. Impaired Excretion

1. Mg and the kidney in renal failure. Reports of hypermagnesemia in renal failure, beginning with that of Mendel and Benedict (303), are numerous even in the early literature (38, 65, 189, 201, 369). Consistent with these observations, it is found that the quantity of Mg excreted usually declines with advancing renal failure (160, 357, 408, 447). Randall *et al.* (357) and Głuszek (160) found an inverse correlation between Mg excretion and creatinine clearance. This decrease is not uniformly observed, however; in the presence of salt wasting, normal or increased excretion of Mg may be observed. In a study of 50 patients with creatinine clearances under 30 ml/min, Popovtzer *et al.* (343) found about two-thirds had diminished Mg excretion, whereas the remainder had normal or increased values.

In addition to decreased excretion, an increase in the fractional clearance of Mg ($C_{Mg}/C_{creatinine}$) is observed with increasing renal failure (46, 95, 160, 343, 344). This increase is particularly marked as the creatinine clearance approaches 10 ml/min. This increase does not correlate with serum Mg (46, 160) and Better *et al.* (46) suggest that the filtered load of Mg is not a major determinant of its clearance. The mechanism of these changes remains poorly understood. Parathyroid hormone decreases Mg excretion and probably does not mediate these effects (383). The ratio of bound to freely diffusible Mg also appears not to change in renal failure (46, 289). Massry and Seelig (289) note that the per nephron excretion of Mg is increased in renal failure (408) and suggest that, under these conditions, the filtered Mg load exceeds the T_m

of Mg producing an increased fractional clearance. Another possible mechanism is suggested by the correlation of fractional Mg excretion with the fractional excretion of sodium (160, 344). Studies have shown that uremic serum contains a humoral factor which causes increased sodium excretion, and it is possible that such a factor may also influence the excretion of Mg (95). Further details are available in the review of Massry and Seelig (289).

2. Chronic renal failure. a. Changes in serum Mg. Patients with chronic renal failure who are not ingesting Mg-containing drugs usually show normal or only slightly increased serum Mg (64, 90, 116, 159, 216, 225, 240, 242, 252, 276, 281, 364, 386, 448). Frank hypomagnesemia has in fact been noted in many patients with chronic renal failure (159, 201, 240, 356, 357, 450). In general, however, both the degree and frequency of hypermagnesemia increase with increasing severity of renal failure. Robinson *et al.* (365) found the threshold for the development of increased levels of Mg to be a glomerular filtration rate below 30 ml/min. In a more recent study, Steele *et al.* (408) found the diseased kidney capable of maintaining Mg homeostasis with an inulin clearance of 10 ml/min. At this level, a fifteen-fold increase in Mg excretion per nephron was observed. Smith and Hammarsten (393) found increases in Mg concentration to be exclusively a function of the stage and not the type of renal disease.

In patients with renal failure who are ingesting excess Mg, hypermagnesemia is common and may reach symptomatic levels rapidly. Randall *et al.* (357) report the onset of symptomatic hypermagnesemia in a uremic patient receiving Maalox (magnesium and aluminum hydroxides) (180 cc/day) for only 3 days. Essentially all reported instances of symptomatic hypermagnesemia in chronic uremia involve the concomitant administration of a Mg-containing enema, infusion, or antacid (17, 42, 161, 190, 201). The use of Renacidin (contains Mg salts) for the dissolution of renal stones has been reported to increase serum Mg levels in the uremic patient (81). Lastly, both excess and depletion of Mg are inducible by dialysis (165) and excessive dialysate Mg has also caused symptomatic hypermagnesemia (145, 163).

b. Changes in tissue magnesium. Total body magnesium is increased in chronic renal failure according to Cantigulia *et al.* (75), who found Mg stores to be increased principally in bone, myocardium, lung, and skin. Bone showed the greatest increase, 66% over normal values, a finding confirmed by Berlyne *et al.* (41) and Alfrey and Miller (16). It is interesting to speculate whether bone offers a readily available storage site for increased Mg loads, and whether variations in the capacity for storage could account in part for the variability of serum Mg in chronic renal failure.

Increased erythrocyte Mg in chronic renal failure has been observed repeatedly (75, 159, 235, 375, 394). Reports concerning the Mg content of skeletal muscle are conflicting. Lim *et al.* (258, 259) reported a decreased mean Mg content in the skeletal muscle of uremics with normal or high serum Mg. This was attributed to chronic Mg wasting and was analogous to the finding of normal serum and depressed intracellular Mg in other studies (137). Cantigulia *et al.* (75), however, reported no difference in the Mg content of normal and uremic skeletal muscle. The conflict remains unresolved.

c. Changes in intestinal absorption of Mg. Mg balance studies conducted by Clarkson *et al.* (90) and Kopple and Coburn (242) indicated that Mg absorption in uremic subjects was essentially the same as in normal subjects. Randall *et al.* (357), however, inferred an increase in the absorption of Mg in their series of hypermagnesemic uremics. Clarkson *et al.* (91) also found such an increase but only in uremics on a high-calcium diet. In marked contrast, however, Brannan *et al.* (63), using *in vivo* perfusion techniques, found not only that Ca had little effect on the absorption of Mg, but also that patients with severe renal disease had significantly depressed Mg absorption. The reason for these conflicting

data is not clear, but resolution of the issue may be of some importance. The use of 1-alpha-hydroxycholecalciferol in renal failure has been reported to increase Mg absorption and produce symptomatic hypermagnesemia (402), although this report, too, is disputed (224).

3. Acute renal failure. Some degree of hypermagnesemia almost invariably accompanies acute renal failure. In a series of 220 patients with acute renal failure but without exogenous Mg intake, Hamburger (174) found a mean maximum serum Mg of 2.6 mEq/liter. The mean maximum in the series of Wacker and Vallee (441) was 3.81 mEq/liter. Nielsen (325) found a mean maximum of 2.75 mEq/liter in a series of acute renal failure patients with a peak occurring early in the diuretic phase. Similar findings have been reported in other clinical (265, 279, 281, 283, 336, 465) and animal (174, 200) studies. The combination of acute renal insufficiency and exogenous Mg intake can produce extremely high levels of serum Mg (313). Acute oliguria accompanied by acidosis may also produce high levels of Mg (316) as in the ketoacidotic patients reported by Martin *et al.* (279, 280) with serum Mg up to 9.3 mEq/liter and in a ketoacidotic patient with accompanying rhabdomyolysis and a serum Mg of 5.5 mEq/liter recently seen at the Peter Bent Brigham Hospital. An important point to be made concerning the hypermagnesemia of acute renal failure and acidosis is that there is a net loss of Mg upon the reestablishment of urinary flow (26, 72, 265). The ensuing hypomagnesemia may have serious consequences, including cardiac arrhythmia and arrest (296).

D. Parenteral Administration

The accidental infusion of significant amounts of Mg has not been reported. Hypermagnesemia following hyperalimentation has been reported but only in uremia (190). Lethal transperitoneal absorption has been observed in humans (292, 313) and confirmed experimentally in the dog (292). In one case (292), a Mg-containing enema was administered to a patient with unrecognized bowel perforation; in another (313), a patient appears to have taken Mg citrate in an attempt to relieve the pain of a perforated ulcer. In rats, Mg-containing talc causes slightly increased serum Mg following abdominal surgery (385). Because Mg readily crosses the placenta (9, 352), the treatment of toxemia with Mg salts occasionally produces significant hypermagnesemia in the newborn (61, 136, 261, 262). Exchange transfusion has been proposed as a treatment for such hypermagnesemic infants (61, 409), but isotope studies show the volume of distribution of Mg to be somewhat larger than the volume of the extracellular space and the efficacy of exchange transfusion is uncertain (261). The kinetics of distribution of Mg have been studied extensively and are reviewed by Aikawa (8). The recently proposed Mg-load test for screening potentially hypomagnesemic infants is said to raise serum Mg by an average of only 0.65 mEq/liter (74).

E. Other Sources

Small elevations of Mg (less than 4 mEq/liter) have been reported with lithium therapy (297), postoperatively (437), in various neoplasms with skeletal involvement (269), hypothyroidism (178, 220, 446), hyperparathyroidism with renal damage, pituitary dwarfism and milk-alkali syndrome (178), and in viral hepatitis (82). In primary hyperparathyroidism alone, negative Mg balance without hypermagnesemia has been reported (35, 179, 237, 430), although very small increases in serum Mg have been seen with experimental administration of parathyroid extract (45, 334). Acute ethanol administration induces hypermagnesemia in the rat (338). There are reports of increased Mg in Addison's disease (197, 442), but no quantitative data are given to document the observations. Elevation of Mg by cortisone in rats has been reported (272) but not confirmed (334).

The mechanism responsible for hypermagnesemia in patients being treated with lithium carbonate is unknown. However, it

is thought to be related to the chemical similarity between the elements (the diagonal relationship). It is presumed that destructive neoplasms of bone release stored magnesium causing both hypermagnesemia and hypermagnesuria. The alterations in patients with hyperthyroidism are presumed to be brought about by the same mechanism.

IV. Effects of Excess Magnesium

A. Effects on the Nervous System

1. The neuromuscular junction. The paralytic effect of Mg has long been recognized (47, 203, 219). Excess Mg affects the peripheral nervous system by suppressing the release of acetylcholine and blocking transmission at the neuromuscular junction (79). It is also known to induce the synthesis of both acetylcholine esterase (147, 317) and acetylcholine (133), to antagonize the effects of Ca (79, 215), and to diminish postsynaptic membrane responsiveness at the neuromuscular junction (79). The spontaneous miniature endplate potential itself is unaffected (80), except in the absence of Ca (210). Competition between Ca and Mg for common receptor sites is thought to play a major role in the effects observed (99, 210, 215, 218). Paralysis of voluntary musculature has been observed in humans (399) and animals (203) at variable concentrations, usually greater than 10 mEq/liter. The respiratory depression following peripheral administration of Mg, once thought to be central in origin (69, 124, 290, 299), is now recognized as peripheral respiratory paralysis and is a cause of mortality in hypermagnesemia. Hypermagnesemic interference with neuromuscular transmission is also a cause of prolonged intraoperative curarization (113, 135, 154, 155, 314). Like curare, Mg may be antagonized by anticholinesterases (66, 274, 318, 407).

2. The autonomic nervous system. As is the case with the neuromuscular junction, excess Mg ion diminishes acetylcholine release and blocks transmission in sympathetic ganglia (215, 405), in vagal terminals of the sino-atrial node (398), at the giant synapse of the squid (425), and in the abdominal ganglion of Aplysia (427). In the bowel, Mg appears to block synaptically dependent myenteric neurons, but not those of the endogenous oscillator type (463). It has been proposed that Mg-induced bowel hypomotility may account for the meconium plug syndrome in the children of Mg-treated toxemic mothers (396). This proposal has been disputed, however, on experimental and epidemiologic grounds (100).

With regard to the sympathetic nervous system, Kirpekar and Misu (238) showed that excess Mg diminishes the output of norepinephrine from adrenergic postganglionic sympathetic fibers. Excess Mg also inhibits the release and facilitates the reuptake of norepinephrine from adrenergic nerve (127) and adrenal medullary granules (263) *in vitro*. In addition, Basbaum (36) has provided cytologic evidence for the failure of apocrine secretion of adrenergic neurosecretory granules in the presence of excess Mg *in vitro*. The synapses of postganglionic sympathetic nerve fibers with smooth muscle have been studied with respect to divalent electrolytes in the isolated vas deferens-hypogastric nerve preparation (54, 250) and in the isolated rabbit ear artery (130). These studies indicate that the actions of Mg and Ca on sympathetic transmission are similar to the actions of these ions on skeletal neuromuscular transmission. It is concluded that Mg probably diminishes the amount of transmitter substance released in addition to diminishing the sensitivity of the postsynaptic membrane to a given amount of the transmitter. The sympatholytic effects of Mg presumably form part of the rationale for its use in the treatment of thyrotoxicosis (180, 211).

3. The central nervous system. In contrast to widely held and persistent beliefs (51, 57, 69, 123, 124, 136, 199, 230, 243, 290, 298, 299, 312, 324, 337), Mg is not an anesthetic nor even a major central nervous system depressant (14, 93, 399, 459) unless given intrathecally or intraventricularly

(132, 134) or applied directly to nervous tissue (226, 227, 232, 247, 257, 400). The most convincing demonstration of this fact was provided by Somjen *et al.* (399) in two volunteers in whom serum Mg levels were raised to 15.3 and 14.6 mEq/liter. Despite profound skeletal muscle paralysis both subjects remained awake and cognizant of pain. This observation is not surprising in light of the demonstration that uptake of Mg from the blood into the central nervous system is quite limited (21, 62, 126, 198, 233, 255, 275, 352, 372). Pritchard (352) reports a toxemic patient whose serum Mg was maintained between 6.3 and 11.0 mEq/liter for 7 days. At the end of that time, her cerebrospinal fluid Mg had risen only to 3.5 mEq/liter (local normal, 2.2 to 2.5 mEq/liter). Doubts concerning the anesthetic efficacy of Mg are, in fact, to be found in older literature (43, 93, 166, 367, 416, 459), and it is interesting to speculate on what basis Peck and Meltzer (337) performed surgery using Mg "anesthesia."

Mg applied directly to the cerebral ventricles does decrease blood pressure and depress vasomotor reflexes (254) and respiration (255). In parallel with observations at the neuromuscular junction, increased Mg has been shown to interfere with synaptic transmission but not spontaneous miniature potentials within the central nervous system (229). Intracellularly applied Mg stabilizes and hence depresses the presynaptic cell membrane (226). On a molecular level, it has been proposed that Mg competes with Ca at Ca-activated potassium ionophores (248). In contrast to most effects in the periphery, Mg and Ca have parallel depressant effects on central synaptic membranes (134, 226).

The use of Mg as an anticonvulsant (48, 49, 312, 461) has largely disappeared, except in the treatment of toxemia of pregnancy. The mechanism of action in convulsive disorders has not been studied in detail. It is reported to be effective when administered either intrathecally (18, 49, 107, 301) or peripherally (312, 353, 461). Given the poor cerebrospinal fluid level obtained following peripheral administration, it would seem likely that different sites of action are involved depending on the route of administration. In the case of peripheral administration, particularly in toxemia, the relative contribution of effects on the autonomic nervous system, the neuromuscular junction, and, possibly, the sensory limb of feedback mechanisms remains to be determined. Central anticonvulsant activity following peripheral administration of Mg is unproven.

Much of the reputation of Mg as an anesthetic and anticonvulsant may have derived from its adjuvant use in conjunction with other agents (4, 106, 167, 246, 351, 359, 373) or with intrathecal administration (18, 49, 107, 184, 301). It has been suggested that hypoxia due to hypotension (43, 367), respiratory paralysis (14), and depression of carotid baroreceptors (399) may contribute to the anesthesia-like state classically described in hypermagnesemia. A report of "hypermagnesemic encephalopathy" in uremia (161) and other reports of altered mental status (357) may reflect secondary rather than primary effects on the central nervous system. It should be noted, however, that central neurons are sensitive to relatively small quantities of iontophoretically applied Mg (226, 227). Thus, either very prolonged hypermagnesmia such as that described by Pritchard (352) or circumstances in which a defect in the blood-brain barrier accompanies hypermagnesemia could lead to central nervous system depression. Lastly, concern has been expressed over the therapeutic use of Mg as possibly injurious in disorders of intracerebral calcification and striatonigral degeneration (117) because of the discovery of Mg in these lesions (118, 119).

4. Nerve impulse conduction. Like calcium, Mg has been shown to increase the threshold of axonal excitation (141). Chronic hemodialysis patients, when changed to a lower dialysate Mg so as to lower plasma Mg, show an increase in nerve conduction velocity (412). Topical application of Mg has been shown to impair nerve

impulse transmission and Mg has been used as a local anesthetic (101, 300). It appears from more controlled studies, however, that very high concentrations are needed (124, 194) and that the effect is probably not specific for Mg.

The neural effects of Mg are summarized in Table 2. Most of these effects are probably due to alterations in the extracellular Mg concentration. They are observed, in hypermagnesemia, as pharmacological effects but these probably represent exaggerations of physiological mechanisms.

B. Effects on the Heart

1. Electrocardiographic and electrophysiologic changes. Excess Mg is known to have several direct and indirect effects on the heart (Table 3). Electrocardiographic observations in humans and animals (149, 165, 309, 357, 366, 390, 417, 451) show an increase in PR interval at concentrations of 5 to 10 mEq/liter which then may progress to complete heart block at levels greater than 15 mEq/liter. His bundle recordings show hypermagnesemia to affect the AH interval (atrium to bundle of His conduction time) to a much greater extent than the HV interval (bundle of His to ventricular muscle conduction time) (149). Such effects are not dependent on intact vagal innervation (435). Intraventricular conduction defects (304, 309, 390, 435) also occur at levels of 5 to 10 mEq/liter Mg. Electrophysiologic studies show excess Mg to shorten the plateau phase of the transmembrane potential, but only if Ca is low (204, 342, 417). Mg, at a concentration of 6 to 15 mM, inhibits contraction and decreases membrane excitability while preserving intracellular action potentials (209). Tall peaked T-waves have been reported in hypermagnesemic uremia (424, 441), but it is not clear that hyperkalemia was not also a factor. Prolongation of the QT interval and diminution of P-wave voltage have also been reported in uremic patients (174, 357). In general, morphologic changes in the electrocardiogram with excess Mg are variable and no classic hypermagnesemic EKG changes have been described (307).

2. Rate and rhythm. Smith *et al.* (390) and Miller and Van Dellen (309) have observed a transient rise in heart rate followed by sinus bradycardia in the anesthetized intact dog with increasing concentration of Mg. Similar observations have been made in humans and other animal species (56, 165, 305, 306, 366, 461), although not with absolute consistency (109, 304). Clinically significant bradycardia may occur in humans with relatively small elevations (4.5 mEq/liter) of Mg (42). Mg has been shown directly to stabilize and slow SA nodal tissue (183, 361, 405, 406, 431); interference

TABLE 3
Common cardiovascular effects of excess Mg

1. Hypotension
2. Transient tachycardia followed by bradycardia
3. Electrocardiographic changes
   a. Increased PR interval
   b. Increased QRS duration
   c. Increased QT interval
   d. Variable decrease in P-wave voltage
   e. Variable degree of T-wave peaking
4. Heart block at high concentration
5. Arrest in asystole at high concentration

TABLE 2
Neural effects of excess Mg

1. Impaired nerve conduction
2. Synaptic blockade
   a. Decreased transmitter release
   b. Diminished postsynaptic responsiveness
   c. Induction of acetylcholine esterase
   d. Increased reuptake of adrenergic transmitters
   e. Competition with calcium for common receptor sites
3. Primary central nervous system depression only if the blood-brain barrier is defective or if applied directly to central nervous tissue.
4. Secondary central nervous depression, in part due to hypotension and hypoxia.

with potassium outflow may be partially responsible (205). Stanbury (405) attributed Mg-induced bradycardia in part to sympathetic cardioaccelerator blockade. Somjen and Baskerville (398), however, have observed a parallel vagal blockade which they attribute to a decrease in the release of acetylcholine, inasmuch as Mg increases the sensitivity of the SA and AV nodes to circulating acetylcholine. Toda and West (431) have noted in studies of isolated atria both pre- and postganglionic blocking effects of Mg in addition to a primary slowing action on SA nodal tissue. Asystolic arrest is reported at concentrations of 17-66 mEq/liter in dogs (305, 309, 390) and as an occasional observation in cases of severe human intoxication (56, 313). It is seldom observed in advance of respiratory arrest, though Randall *et al.* (357) report an instance of asystolic arrest at 4.8 mEq/liter in a patient receiving digitalis.

Mg has been studied as an antiarrhythmic agent in both supraventricular and ventricular tachyarrhythmias (59, 112, 125, 471). Its use as an antiarrhythmic has largely been abandoned in this country except in the instance of digitalis-induced arrhythmia, where it appears to be efficacious and remains under investigation (153, 321, 380, 381, 388, 403, 406, 419). This recent enthusiasm for Mg in digitalis toxicity contrasts with older reports that in the presence of digitalis Mg can worsen heart block and induce ventricular ectopic activity (310). Its mechanism of action in this setting is unclear (403), but it is recognized that hypomagnesemia is common in patients treated with digitalis (40), and perhaps Mg is of use only if hypomagnesemia is present. The mechanism of such hypomagnesemia is also unclear. Concomitant treatment with diuretics may be one factor. It is reported that cardiac glycosides decrease the renal tubular absorption of Mg (282), but it has also been observed that correction of congestive failure (270) or digitalis toxicity (236) can correct hypomagnesemia without supplemental Mg. In some centers in Europe, Mg is actively employed in coronary care units to treat tachyarrhythmias regardless of etiology (76, 98, 266), and there is a recent report of the successful use of Mg in the treatment of lithium-induced arrhythmia (464). Given the recent association of decreased Mg with myocardial infarction (2, 85), the morbidity of infarction-related arrhythmias, and the widespread use of digitalis, it would seem that further evaluation of the safety and efficacy of Mg as an antiarrhythmic is warranted.

3. Contractility and cardiac output. In general, the effects of Mg on contractility are not great provided Ca concentration is normal (148, 244, 256). The indirect effect of Mg-induced hypocalcemia (*v.i.*) may be postulated to affect contractility in chronic hypermagnesemia, but this has not been demonstrated. The inotropic effects of epinephrine are preserved in the presence of increased Mg (256, 331) despite blockade of epinephrine-induced glycogenolysis. The latter effect is reversible with Ca. Several studies of the isolated heart have reported that Mg is a coronary vasodilator (37, 323, 377, 406, 421), but these have not been supported by study of the intact animal (291). With respect to cardiac output in intact animals, Maxwell *et al.* (291) found no diminution in output at concentrations of Mg sufficient to produce significant hypotension. Aldrete *et al.* (14), however, report significant elevation of central venous pressure with hypermagnesemia of 14 mEq/liter in the awake animal, but do not provide other information on the physiologic status of the animal at that level of hypermagnesemia. A recent study of humans utilizing systolic time intervals (103) found that although Mg given as a bolus (2.5 g $MgSO_4$ over 30 sec) diminished myocardial performance somewhat, when given as a constant infusion (30–50 mg/min) it had no effect on performance. The role of Mg and Mg therapy in cardiomyopathy, atherogenesis, angina, coronary artery disease, and sudden death remains under study (2, 5, 85, 138, 212, 273, 379, 420).

C. Hypermagnesemic Hypotension and Related Issues

1. Introduction. Hypotension attributed to hypermagnesemia has been reported in both humans and animals, although its incidence, severity, and duration have been found to be variable. Pharmacological studies were carried out by Winkler *et al.* (461), who infused Mg into a series of normal volunteers and patients with renal, cardiovascular, and hypertensive diseases. They found that about half of all subjects showed some degree of hypotension during the infusion. In normal subjects, the blood pressure fall was often precipitous; hypertensive subjects most often showed no blood pressure change; patients with eclampsia and acute nephritis showed the most consistent fall in blood pressure. In most instances, they report rather prompt return of blood pressure to control levels following discontinuation of the infusion but before serum Mg levels had returned to normal. Kelly *et al.* (231) observed little blood pressure change in humans given Mg infusions, but did note some fall in normal and hypertensive subjects given Mg as a bolus. Randall *et al.* (357) and Alfrey *et al.* (17) observed persistent hypotension in humans as an early manifestation of uremic Mg intoxication following antacid ingestion. Hypotension was variably observed at concentrations of 3 to 5 mEq/liter, and consistently observed at higher concentrations. Hypotension has not invariably been reported during brief hypermagnesemia in supine test subjects, however (357, 399, 461), and orthostatic hypotension has been noted in the absence of supine hypotension (357). There are additional isolated reports of possible hypermagnesemic hypotension in the clinical literature (56, 165, 313), and Mg was once used to treat the hypertension of acute glomerulonephritis (368). Modern studies show that in toxemia, Mg produces only transient and unpredictable lowering of the blood pressure (353). At concentrations lower than those commonly associated with hypotension, Mg can produce intense cutaneous vasodilatation in humans (131, 461). Plethysmographic studies (187) have demonstrated dilatation of deeper vascular structures. Indicator dilution techniques have revealed decreased peripheral vascular resistance in both normal and hypertensive humans following local infusion of Mg (329). Not surprisingly, the question of a disturbance of Mg metabolism has been raised, but not resolved, with regard to the pathogenesis of human hypertension (11, 170, 171, 329, 339, 382, 420).

Hypotension in unanesthetized animals was reported in very early investigations of Mg (298). In anesthetized dogs, Hoff *et al.* (202) noted hypotension at 2 to 5 mEq/liter Mg. The fall in blood pressure became more profound with increasing Mg levels until lethal respiratory arrest supervened at 15 to 25 mEq/liter. This finding has been noted but not well documented in cats (367) and rabbits (43), and has been more recently replicated by Maxwell *et al.* (291) in the anesthetized dog and by Aldrete *et al.* (14) in the unanesthetized intact dog. In contrast, however, Dandavino *et al.* (109) found only transient hypotension and no other significant hemodynamic effects of sustained hypermagnesemia in normotensive and renal hypertensive pregnant sheep.

In interpreting the animal data, it is difficult to segregate out the influence of anesthesia, species-specific variation, and other differences in experimental design. Similarly, in the human studies, the contribution of intercurrent illness, route of administration, and individual differences in determining susceptibility to hypermagnesemia is unclear. Some degree of hypotension is evident in most studies, however, and consideration of possible mechanisms of action would seem to be worthwhile despite the complexity of the problem.

2. Vascular smooth muscle. Decreases in vascular resistance not attributable to hypertonicity (360) have been noted following hypermagnesemia in the denervated isolated dog liver (86), the mesenteric vascular bed of the dog (108, 428) and rat (152), the renal vascular bed (146, 156), and the iso-

lated dog forelimb (146, 169, 330). Decreased responsiveness of bronchi (185) and isolated intestinal (467) and vascular (19, 176, 404) smooth muscle has been reported with increased Mg. Reports of Mg as a coronary vasodilator have been noted above. In isolated cat gracilis muscle, Viveros and Somjen (438) have shown that the decrease in vascular resistance induced by Mg cannot be fully reversed by tonic nerve stimulation, administration of Ca, or by application of norepinephrine, all of which would be thought to be effective vasopressive maneuvers if some form of neural blockade alone were responsible for the vasodilatation. Three separate aspects of muscle contraction must be considered in attempting to account for these findings: excitation, excitation-contraction coupling, and the contractile mechanism itself. There is some evidence that all three may be affected by excess Mg, but much of it is tenuous.

The excitability of vascular smooth muscle membrane is depressed by Mg *in vitro*. Bohr (52) has observed that both Mg and Ca, in a concentration of 6 mM, inhibit the fast component of vascular smooth muscle contraction and notes that membrane excitation appears to be the rate-limiting step depressed by the excess ion. At 30 mM Mg, however, Sperelakis (404) has observed field contraction action potentials despite arrest of the mechanical activity of intestinal smooth muscle. Viveros and Somjen (438) call into question the importance of membrane excitability changes in the *in vivo* preparation because of their experimental observation that Mg and Ca act antagonistically, not synergistically, on resistance vessels and blood pressure. They note that other investigators have shown that Mg and Ca ions act synergistically to depress smooth muscle (52, 250), skeletal muscle (162), nerve fiber (141), and nerve soma (226, 227) electrical activity. Viveros and Somjen propose that Mg interferes with excitation-contraction coupling. They hypothesize that Mg inhibits the entrance of Ca ions from the extracellular space following membrane excitation, thereby impeding the initiation of contraction. A similar proposal had been made earlier by Bozler (60), and has recently received additional support (128, 162, 234, 326, 348).

A direct interference with the contractile mechanism must also be considered. Mg has both an enhancing and a depressant effect on smooth muscle contraction, although the latter predominates as Mg concentration increases (53). Mg can activate glycerol-extracted smooth muscle in the presence of ATP (53), and it has been proposed that a Mg-ATP complex is a component of all ATP reactions (423). However, excess Mg may actually inhibit vascular myosin ATPase (150, 395), possibly by chelate formation (71). The effect of excess Mg on contractile proteins *in vivo* appears in doubt, however, because of the large stores and tight regulation of intracellular Mg. Wallach *et al.* (445–447) have shown that the intracellular concentration of Mg is relatively stable in the setting of acute excess Mg. In particular, the intracellular concentration of Mg in vascular smooth muscle has also been shown to be preserved in the face of acute hypermagnesemia provided that ATP-dependent sodium pumps are functional (333). Further, symptomatic hypermagnesemia has been reported to coexist with intracellular hypomagnesemia (258, 259). However, entrance of Mg into cells subject to chronic excess Mg has been noted (326). In addition, work by Nanninga (319, 320) has raised the issue of whether increased free intracellular Mg as a function of activity may play a role in the depression of response in fatigued muscle (53). If so, perhaps even small changes of intracellular Mg may produce decreased contractility.

3. The peripheral nervous system. Inasmuch as a direct depressant effect of excess Mg ions on vascular smooth muscle seems established, the possibility of neurotoxicity must also be considered. Excess Mg is known to affect both the voluntary and autonomic peripheral nervous systems as outlined earlier. Accordingly, there are sev-

eral potential forms of Mg-induced neural toxicity pertinent to the development of hypotension.

a. Sympathetic blockade. Hutter and Kostial (215) and Stanbury (405) have shown Mg to be an effective sympathetic blocking agent in the heart-lung preparation. Sympathetic blockade has, therefore, been invoked as an explanation for hypermagnesemic hypotension (124, 405). Even though hypermagnesemic sympathetic blockade has been well established, however, its importance in the intact animal remains inferential and questionable. Indirect support for a role came from observations on the effectiveness of Ca and anticholinesterases in reversing some of the effects of severe Mg intoxication. Aldrete *et al.* (14) report that a combination of neostigmine and pentylenetetrazol, a mixture historically believed useful in reversing Mg "anesthesia" (57), is capable of reversing Mg-induced hypotension in the dog. Physostigmine (223, 407) and other antagonists of curare are also said to be effective as global antagonists of Mg. With regard to hypotension, however, all such reports suffer from the possibility that the agent played only an indirect role, reversing respiratory paralysis, for example, rather than acting directly on ganglionic transmission. Against a significant role for sympathetic blockade are early experiments demonstrating hypermagnesemic hypotension in decerebrate dogs and in frogs with the spinal cord destroyed (186). Stanbury (405), in cats with the spinal cord destroyed, using epinephrine to maintain blood pressure, still was able to show a drop in blood pressure with administration of Mg. More recently, in the intact anesthetized dog, Maxwell *et al.* (291) induced hypotension with Mg and measured several other hemodynamic parameters. In contrast to studies employing classical ganglionic blocking agents such as hexamethonium (104), they could demonstrate no change in cardiac output, cardiac work, or coronary blood flow. Translation of these findings into the clinical setting is a difficult task, however, and it may be that sympathetic blockade does play some role in hypermagnesemic hypotension, particularly in the development of orthostatic hypotension.

b. Skeletal neuromuscular blockade. Excess Mg affects skeletal muscle both by neuromuscular blockade and direct effects on the muscle. Excess Mg increases intracellular Mg and depresses contractility (25, 234, 326) without affecting membrane potential (295). Mg-induced paresis of large skeletal muscle groups could permit venous pooling and diminution of venous return and cardiac output. The process might possibly be relevant to the development of orthostatic hypotension.

c. Diminished release of adrenal catecholamines. This mechanism has been proposed by Maxwell *et al.* (291). It may be viewed as a special case of ganglionic blockade or as a direct effect of Mg on the adrenal medullary cell (263). As an explanatory mechanism for hypermagnesemic hypotension, its limitations are the same as those of the general cases detailed above.

4. The central nervous system. When simply injected into the cisterna magna, Mg has little effect on blood pressure (363), but perfusion of the cerebral ventricles with Mg does depress blood pressure and vasomotor reflexes (254). Stanbury (405), however, demonstrated that intracarotid injections of Mg cause an increase in blood pressure. More importantly, it has already been described above that uptake of Mg from the blood into the central nervous system is limited, and it is unlikely that central effects play an important role in clinical hypermagnesemic hypotension.

5. Depression of the carotid baroreceptor. Heymans and Capet (196) have demonstrated abolition of the pressor response to bilateral carotid occlusion in the mildly hypermagnesemic normotensive dog. This pressor response could be restored by Ca. Eyzaguirre and Koyano (129) demonstrated depression of carotid baroreceptor output after exposure to 10 mEq/liter Mg. The significance of these findings in relation to hypotension is unknown, although it has

been suggested by Somjen *et al.* (399) that it may relate to the apparent tranquility of animals and humans subjected to Mg-induced hypotensive ischemia.

6. Cardiotoxicity. The cardiotoxic effects of Mg have already been described in some detail. The relative importance of such effects in the development of hypotension is not entirely clear, however. As noted earlier, Maxwell *et al.* (291) reported hypotension with normal cardiac output, but the dogs were anesthetized. Aldrete *et al.* (14) found hypotension in unanesthetized dogs but also noted a rise in central venous pressure suggesting failure. Dandavino *et al.* (109), on the other hand, using unanesthetized sheep, found only transient hypotension and failed to note the bradycardia that usually accompanies serious hypermagnesemia. Note has previously been made of the human study showing a transient decrease in cardiac performance as measured by systolic time intervals following boluses of Mg (109), and the observation that hypotension in normal humans tends to be transient (231, 461). Taken together, these data suggest that whatever is the primary source of hypermagnesemic hypotension, some form of myocardial compromise may be required for its maintenance. In clinical terms, some intercurrent illness may be required to sustain hypotension with small elevations of Mg. Clearly, however, in the case of exposure to high concentrations of Mg for prolonged periods, disturbances of rhythm and performance play a major role. More research on the hemodynamic consequences of hypermagnesemia is needed.

7. Antagonism of Mg-induced effects. Calcium has long been recognized to antagonize Mg (66, 274, 302). The principal form of use has been as an antidote for the respiratory depression of hypermagnesemia. In the intact animal, Ca has been shown to reverse hypermagnesemic hypotension rapidly and consistently (14, 291). In the treatment of human eclampsia with $MgSO_4$, Ca is used to treat hypotension and respiratory paralysis (353, 470). It has also proven transiently effective in a number of isolated case reports of Mg poisoning (17, 97, 131, 259, 262, 313, 357, 410). Its use in clinical practice continues to be recommended (260), although it may be less effective in the neonate (261) than the adult. Other accounts of the experimental use of Ca and anticholinesterases as antagonists of Mg have been described above.

There are few studies of common pressors in the setting of hypermagnesemic hypotension in humans or intact animals. Isoproterenol and levarterenol have been reported to be ineffective in a case of severe human hypermagnesemic shock (313). There is a report that Mg diminishes sensitivity to the pressor effect of angiotensin (418). Several *in vitro* studies tend to confirm that Mg reduces but does not eliminate entirely the responsiveness of vascular smooth muscle to catecholamines. George and Leach (152) report Mg to interfere with the vasoconstrictor effects of catecholamines in perfused rat mesentery. Haddy (169) observed decreased responsiveness to norepinephrine in the hypermagnesemic dog forelimb. Farmer and Campbell (130) report diminished sensitivity to norepinephrine and to both the direct and indirect effects of tyramine in the rabbit ear artery. In isolated cardiac muscle, increased Mg has been reported not to block the inotropic effects of epinephrine (256, 331). Physiologic concentrations of Mg appear to potentiate alpha but not beta responses of smooth muscle to isoproterenol (432), but the effects of excess Mg on such a system have not been studied. Lastly, vasopressin responsiveness is also diminished by excess Mg (438), a finding which contrasts with the potentiation of neurohypophyseal peptide effects on smooth muscle by Mg in physiologic concentrations (401).

D. Effects on the Normal Kidney and Electrolyte Transport

The effects of acute hypermagnesemia on glomerular filtration rate (GFR) and renal plasma flow (RPF) in the normal dog kidney tend to be small and not consistently observed (87, 182, 241). In both normal and

toxemic humans, a decrease in GFR has been described with increased Mg (20, 175, 193), but again the effects are not uniformly reported (231, 352). Kelley *et al.* (231) found Mg infusions to increase RPF in normal subjects. Hammarsten *et al.* (175) observed the opposite. In renal failure, excess Mg may decrease RPF but not GFR (175). Hypermagnesemia decreases both sodium and water reabsorption in the rat kidney (114), and an analogous effect is observed with regard to intestinal absorption of sodium (115). Excretion of a Mg load is also accompanied by increased excretion of Ca, sodium and chloride (231) and a variable change in the excretion of potassium (84, 231). An earlier suggestion that hypermagnesemia leads to hypokalemia (391, 392) appears never to have been substantiated. The effects of hypermagnesemia on the renin-angiotensin system have not been studied in detail. $MgCl_2$ infusions into the renal artery *in vivo* can both depress blood pressure and stimulate renin independent of blood pressure changes (87). Release of renin by Mg infusion in the perfused rat kidney has also been demonstrated (144). Mg infusion into sodium-depleted humans does not, however, affect plasma renin (239).

E. Effects on Blood Clotting

Excess Mg (or more generally, an increased Mg to Ca ratio) interferes with platelet adhesiveness (58, 111, 212), thrombin generation time (213), and clotting time (24, 151, 397). It may also increase fibrinolysis (468). A postulated relationship between hypomagnesemia and coronary occlusion has led to the advocacy of Mg as an adjuvant and prophylactic in cardiovascular disease (212, 362). Mg has been claimed useful in treating peripheral vascular disease (168, 376), but such claims are disputed (374, 454, 460). It has been suggested that uremic clotting disorders may in part be due to chronic excess serum Mg (111). The topical application of Mg has been investigated as a measure to assure the patency of microvascular anastamoses (3).

F. Effects on Endocrine Systems

Hypermagnesemia has been documented to induce hypocalcemia both in animals (158, 241, 345, 347, 355) and humans (222, 231, 315), particularly in the Mg-treated toxemic mother (121, 311) and her progeny (371). This effect is felt to be mediated at least in part by diminished parathyroid hormone secretion (70, 158, 288, 341, 384, 426) and possibly by altering end organ responsiveness to parathormone (389). The effect is also seen in patients with parathyroid insufficiency (222), however, and presumably other mechanisms remain to be defined. The parathyroid hormone-suppressing effect of Mg in the dog is less potent than that of Ca (288).

Both indirect evidence (31, 308, 345, 347, 355) and radioimmunoassay studies (77, 264, 354) suggest that an increased level of calcitonin may also play a role in Mg-induced hypocalcemia. In humans with medullary carcinoma of the thyroid, however, Mg has produced a lowering of serum calcitonin (22). The discrepancy between this finding and the animal data is as yet unresolved.

As to other endocrine effects, Mg infused into the renal artery has been reported to stimulate renin secretion in the dog (87) and rat (144), but Mg infusion in the sodium-depleted human does not affect plasma renin (239). Although, as noted earlier, Mg is sometimes used in hyperthyroidism (180, 211, 322), Mg infusions have been shown to have no consistent antagonistic effect on the peripheral functions of thyroid hormone (462). Lastly, Mg has been reported to stimulate gastrin release in a patient with gastrinoma (110).

G. Effects on Bone

The Mg content of bone is considerably increased in uremia (16, 41, 75). Berlyne *et al.* (41) found 3.3 mg Mg per g dried bone in uremic patients as compared with 2.6 mg per g in normal subjects. This increase is thought to be principally a function of increased serum Mg (16, 105). Only 30% of

the increased Mg is in the surface-exchangeable pool of bone, and it is only this fraction that normalizes after renal transplantation (16). More importantly, an excess of Mg has been known for some time to produce abnormal bone (105). Posner (349) and Bachra *et al.* (28) found that Mg stabilizes amorphous calcium carbonates and phosphates and disturbs apatite crystalization. In some animal models, even a simple increase in dietary Mg may produce histologically abnormal bone (88), and excess Mg also potentiates soft tissue calcification in vitamin D-treated rats (457). Accordingly, it has been speculated that Mg may play a role in renal osteodystrophy inasmuch as Mg can influence both crystal size and stability (16).

As noted in the preceding section, Mg is known to decrease secretion of parathyroid hormone. Not surprisingly, therefore, increasing dialysate Mg so as to increase serum Mg and suppress parathyroid hormone has been investigated as an adjuvant in the prevention of renal osteodystrophy (340, 341). Katz *et al.*, however, found that 9 of 10 patients with renal failure and secondary hyperparathyroidism nonetheless had mild elevations of serum Mg (228). The reports of abnormal bone with increased Mg would thus make it seem prudent to avoid high Mg dialysate until more is known of the pathophysiology of renal osteodystrophy.

H. Effects in Toxemia of Pregnancy and on Uterine Muscle

The efficacy of intrathecal and intravenous Mg salts in the treatment of toxemia of pregnancy, beginning with the report of Horn (207), has been recognized for some time (18, 251), and Mg remains a useful treatment modality (83, 353, 378, 470). However, inasmuch as the mechanisms responsible for the development of the condition remain obscure, the mechanism of action of Mg remains speculative and its use empirical. There is a slight depression of serum Mg in pregnancy but no difference between normal and toxemic pregnancies (172). It appears on the basis of recent data that the major utility of Mg is in the treatment of convulsions and not in the lowering of blood pressure. Dandavino *et al.* (109) found no significant hypotensive effect of Mg in a study of normal and renal hypertensive pregnant sheep. In their series of 154 eclamptic patients, Pritchard and Pritchard (353) also noted only a transient hypotensive effect of Mg and emphasize the use of hydralazine for blood pressure control. The reason the discrepancy between these recent observations and the older reports of a consistent reduction of blood pressure in eclamptics by Winkler *et al.* (461) and others is unclear. Although the use of Mg is generally held to be without serious consequences on uterine contractility or the intrauterine fetus (214), there are reports of decreased contractility of uterine muscle and prolonged labor in the Mg-treated mother (173, 181, 249). There are also reports of symptomatically hypermagnesemic neonates (61, 136, 261, 262). Other studies, however, have indicated that symptomatic neonates are uncommon (413) and may occur only in instances where the mother was treated with intravenous infusions of Mg up to the time of delivery, rather than with intermittent intramuscular injections (261). Pritchard and Pritchard (353), in their series, report no deaths among fetuses weighing at least 1800 g and alive at the start of Mg therapy. Their standard regimen consisted of an initial intravenous bolus of 4 g $MgSO_4$ over not less than 3 min followed by 5 g intramuscular injections immediately and every 4 h thereafter. Each injection was contingent upon the presence of deep tendon reflexes, adequate urine output, and unlabored respirations. Other institutions do allow for constant intravenous infusions of $MgSO_4$ (1–2 g/hr) in place of the painful injections (139, 378). The major arguments against doing so are the association of the intravenous route with a higher rate of complications, the need for fastidious attention to infusion rates, and widespread familiarity with the intramuscular regimen.

Excess Mg diminishes spontaneous uter-

ine activity (92) and has been used as a relaxant for the tetanically contracted gravid uterus (1). In physiologic concentrations, Mg enhances uterine response to oxytocics (142, 245). Estrogens appear to increase the Mg content of the uterus (443), and increased Mg may account for estrogen enhancement of the effect of oxytocin (44).

V. Clinical Implications

A. Recognition of Toxicity

As long as the use of Mg continues to be widespread—and our fascination with it has persisted since the discovery of the Epsom Spring—its toxic effects will occasionally be encountered. Hypermagnesemia is most often recognized in the uremic patient, where it is most frequently suspected. Serum Mg must be determined in all instances of acute renal failure and should probably be monitored periodically in patients with chronic renal insufficiency. In the absence of uremia, detection of hypermagnesemia may be difficult on the basis of clinical signs alone. It should be considered in all cases of severe acidosis and hypotension. It may be particularly useful to suspect Mg as an "unmeasured cation" in instances of low anion gap in stable patients, and normal anion gap in severely ill acidotic patients (122).

The toxic effects of hypermagnesemia (Fig. 1) are manifest as a sequence of changes observed with increasing concentration (357). The earliest observations are hypotension, nausea, and vomiting at concentrations of 3 to 9 mEq/liter. Because these early symptoms of hypermagnesemia are not dissimilar from those of uremia, the diagnosis may easily be overlooked. Urinary retention due to failure of micturition reflexes is also observed at these levels (357). In patients with renal failure, such retention might well compound the renal failure and thereby worsen the hypermagnesemia. Bradycardia may also be observed at this concentration (42) as may cutaneous vasodilatation (131, 461). Electrocardiographic changes, hyporeflexia, and secondary central nervous system depression are the next major manifestations at 5 to 10

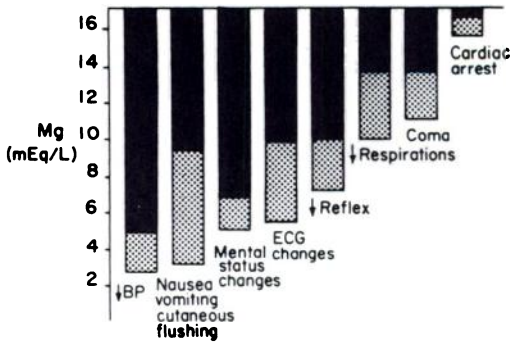

FIG. 1. The stippled areas represent levels of inconstant symptomatology and the solid portions of the bars represent levels where symptoms are commonly present. Modified from *Randall et al.* (357).

mEq/liter. Approximately the same sequence of changes is observed in the neonate (262). Respiratory depression and coma are observed above 9 to 10 mEq/liter; asystolic arrest may occur above 14 to 15 mEq/liter.

B. Treatment

Immediate but transient reversal of toxicity may be effected with calcium. Anticholinesterases have been reported useful in older literature. Dialysis is the treatment of choice. Both peritoneal (55, 235, 370, 465) and hemodialysis (50, 327) are capable of controlling hypermagnesemia. Mg losses are dependent on the dialysis gradient and losses as high as 700 mg per dialysis have been reported (375). A dialysate concentration of about 1.0 mEq seems to yield consistent normalization of serum Mg (50, 411) in chronic renal failure. Higher concentrations can produce chronically elevated serum (375) and erythrocyte Mg (271). Acute magnesium excess and depletion are inducible by Mg (165), and symptomatic hypermagnesemia has been produced by excessive dialysate Mg (145, 163). Appropriate dialysis also reduces both erythrocyte (235) and skin (286) Mg.

C. Prevention

Most instances of symptomatic hypermagnesemia involve the use of Mg-containing drugs, and prevention requires little

more than thoughtfulness in the use of "safe" drugs: the Mg-containing antacids and laxatives. Controlled therapeutic increases in Mg are useful in toxemia and may prove useful elsewhere. Here only fastidious attention to clinical signs and the monitoring of levels will provide the needed margin of safety. In the treatment of deficiency states, the extracellular deficit is replaced in divided doses over a 48-hr period. Replacement therapy is often given intramuscularly but may be safely given using an intravenous infusion pump.

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