



## DISORDERS OF MAGNESIUM: MAGNESIUM DEFICIT AND EXCESS

*Shane Bateman*

Historically, magnesium has received very little attention in veterinary medicine as an electrolyte worthy of consideration. Studies conducted in animal models in the early twentieth century documented the devastating effects of dietary magnesium deficit in dogs.<sup>22,23,111,157</sup> For the ensuing decades, magnesium did not receive any significant attention. Dietary magnesium became a topic of interest in the 1970s and 1980s as a potential risk factor for cats with struvite urolithiasis and urethral obstruction.<sup>28,87,120</sup> Today, following significant study of the syndrome in cats and identification of numerous other risk factors, magnesium in the diet is no longer considered a risk factor for the formation of feline urolithiasis.<sup>20,21,52,85</sup> Since then, magnesium research in veterinary medicine has begun to document some of the clinical issues related to magnesium, but more work is needed.

Veterinary critical care has made significant developmental strides during the past 20 years as it follows in the footsteps of its human counterpart discipline. Magnesium has gained considerable importance within the discipline of critical care because of the prevalence of magnesium-related metabolic dysfunction documented in human and veterinary patient populations. Study of magnesium-related disease has proven to be difficult, most likely because approximately 99% of the body's magnesium is stored inside the cell, where it participates in vital behind-the-scenes metabolic activities of the cell. As technology has advanced, however, our understanding of the important role magnesium plays in maintaining normal homeostasis of body systems, such as the cardiovascular and neuromuscular systems, has increased significantly. At the beginning of the twenty-first century, the field of magnesium study is rich and ripe with opportunities. Our efforts have only just begun to scratch the surface of understanding the importance of magnesium.

## MAGNESIUM REGULATION AND BALANCE

### DISTRIBUTION OF MAGNESIUM

The precise distribution of magnesium in the bodies of dogs and cats under differing conditions has not been well studied. The distribution of magnesium within the bodies of humans has been documented more effectively. In humans, current estimates suggest that only about 1% of the total body magnesium is located outside the cell in the extracellular fluids (ECFs) and that the remaining 99% is located in intracellular stores.<sup>119</sup> Approximately two thirds (67%) of body magnesium is stored in the bone with calcium and phosphorus, 20% is found in muscle tissue, and 11% is found in other soft tissues not including muscle.<sup>117</sup> Bone and muscle account for the major intracellular stores of magnesium in humans. Exchange between intracellular magnesium and the ECF is difficult to study, but current estimates suggest that only 15% of these stores are considered to be exchangeable with the ECF. It appears that bone, muscle, and red blood cell stores of magnesium are very slow to liberate magnesium to the extracellular pool, and that soft tissues are much more able to liberate magnesium to the extracellular space in humans.<sup>119</sup> In dogs, however, similar radioisotope studies suggest that bone magnesium is the most labile pool and will be scavenged during a magnesium deficit.<sup>13</sup> Regulatory control of magnesium shifts between intracellular and extracellular spaces is poorly understood and is likely to be complex and multifactorial. Extracellular magnesium is present in three forms (like calcium): an ionized or free form (55%) that is thought to constitute the biologically active fraction, a protein-bound form (20% to 30%) and a complexed form (15% to 25%). Unlike calcium, which is approximately 40% protein bound, magnesium is only 20% to 30% bound to protein and so is less affected by changes

in albumin concentration.<sup>84,117</sup> Inside the cell, magnesium is complexed to many organic compounds where it plays a pivotal role. Current estimates indicate that only about 1% to 2% of the intracellular magnesium is present in the ionized or free form. Presumably, magnesium also shifts between the free and complexed intracellular forms as well, but the precise regulatory mechanisms governing those shifts are not understood at this time.

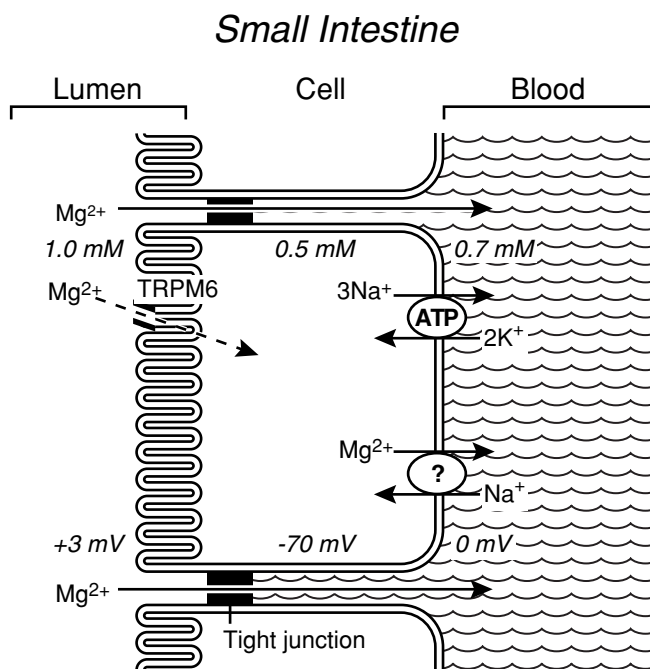
### GASTROINTESTINAL HANDLING OF MAGNESIUM

The primary site of magnesium absorption appears to be the ileum, but the jejunum and colon also contribute substantially to net absorption.<sup>63,65</sup> The mechanisms of magnesium absorption from the ileum are the most well studied at this time. Much research remains to completely understand the complexities of gastrointestinal magnesium absorption. Several key mechanisms are currently well understood. Two pathways for intestinal magnesium absorption exist: an unsaturable passive paracellular route and a saturable active transcellular route (Fig. 8-1).<sup>63,65,74</sup> The paracellular movement of magnesium occurs through the tight junctions between epithelial cells. The driving forces for paracellular magnesium movement are the transepithelial magnesium concentration gradient, the transepithelial voltage gradient formed

by salt and water absorption, and the permeability of the tight junctions to magnesium.<sup>75</sup> The transepithelial concentration gradient generally favors absorption of magnesium from the gut and is influenced by the gut intraluminal ionized magnesium concentration (chelated or complexed magnesium species do not contribute). Thus total dietary intake of magnesium and intake of dietary constituents that influence the amount of magnesium that is complexed or chelated may influence the net absorption of magnesium. Net movement of salt and water creates the transepithelial voltage gradient. A small positive intraluminal voltage results in a small force favoring transepithelial cation movement. Solvent drag created by sodium and water reabsorption will also result in transepithelial movement of magnesium and other ions. Therefore water and salt reabsorption from the gut have a significant influence on magnesium absorption.

The permeability of the paracellular tight junctions is currently an area of intense study and interest. Numerous proteins exist in the tight junction that serve as ion channels and influence permeability of many ions. Specific magnesium ion channels in the gut epithelial tight junctions have not been conclusively identified. Proteins regulating magnesium movement through the renal epithelial tight junctions have been identified (paracellin-1 [PCLN-1]), leading to speculation that a similar protein may exist in the gut as well. Once identified conclusively, further study will be required to determine whether this tight junction protein is selectively permeable and under what influences such selectivity is expressed.

Active transcellular magnesium movement from the gut is an area of very recent and exciting discovery. Study of numerous inherited conditions of impaired magnesium handling in humans led to an improved understanding of magnesium transport across the gut epithelium and a hypothesis that several magnesium transport proteins exist in both the luminal and basolateral cell membranes of gut epithelial cells.<sup>31</sup> Identification of two very unique ion channels has only recently occurred. A unique family of genes called the transient receptor potential (TRP) family codes for both proteins. Both proteins are in the M subfamily and are labeled TRPM6 and TRPM7, respectively. TRPM6 and TRPM7 are found extensively in membrane surfaces of the small intestine, colon, and distal collecting tubule of the kidney, all sites that are involved in magnesium regulation.<sup>80,99,139</sup> These two proteins are unique because they are the only known ion channels that combine a protein channel with an intracellular protein kinase or enzyme. As a result, much speculation has occurred about the role of the attached enzyme in magnesium homeostasis.<sup>80,99,139</sup> One study suggests that magnesium-adenosine triphosphate (Mg-ATP) is the substrate for the enzyme portion of these channels, resulting in inhibition of magnesium entry through the channel into the cell.<sup>100</sup> This finding has led to speculation that increasing intracellular levels of magnesium are able to thus



**Fig. 8-1** Magnesium handling in the small intestine. Paracellular transport of magnesium occurs via tight junctions down a favorable electrochemical gradient. Transcellular transport of magnesium occurs down favorable electrochemical gradients into the cell and is postulated to occur through TRPM6 channels. The net movement of sodium and water favors the net reabsorption of magnesium.

inhibit intracellular entry of magnesium through this mechanism and that this constitutes the energy requiring active transport mechanism of transepithelial magnesium transport. Alternatively, others speculate that magnesium movement into the cell through TRPM6 and TRPM7 occurs via a favorable voltage gradient and that the active phase of magnesium transport across the cell occurs at the basolateral membrane, possibly connected to active sodium-magnesium exchange.<sup>75</sup>

In the kidney, calcium and several additional hormones influence transcellular and paracellular magnesium transport mechanisms. It is likely that similar control mechanisms influence magnesium reabsorption in the gut. The specific actions of each of these influences and the precise mechanisms of action have yet to be established. The influence of calcium and hormones on the renal handling of magnesium is much better studied and understood. However, some evidence does exist to support the positive influence of parathyroid hormone (PTH) and 1,25-dihydroxycholecalciferol ( $1,25[\text{OH}]_2\text{D}_3$ ) levels on reabsorption of magnesium from the gut.<sup>64,82</sup>

The percentage of magnesium absorbed by transcellular and paracellular mechanisms depends primarily on the dietary concentration of magnesium. When magnesium intake is high, then a large concentration gradient exists, and most absorption likely occurs through the paracellular route with small quantities absorbed across the cell. Conversely, when magnesium intake is poor and a low concentration gradient exists, paracellular magnesium transport is less efficient, and active transcellular magnesium transport plays a much larger role in maintaining adequate magnesium balance.

## RENAL HANDLING OF MAGNESIUM

Although the gut plays a crucial role in magnesium balance, the kidney is the site of control and regulation of magnesium balance. Various segments of the nephron play an important role in magnesium homeostasis. Numerous hormonal and other influences also play a role in the maintenance of magnesium balance. The complex interactions of many factors that may influence each other are the focus of intense research. Two factors have greatly assisted in elucidating the cellular physiologic principles guiding magnesium handling by the kidney. Genetic mapping and the accompanying molecular biological technology combined with investigation of several rare inherited renal magnesium handling disorders have contributed to new breakthroughs in the understanding of renal magnesium handling.

### Proximal Tubule

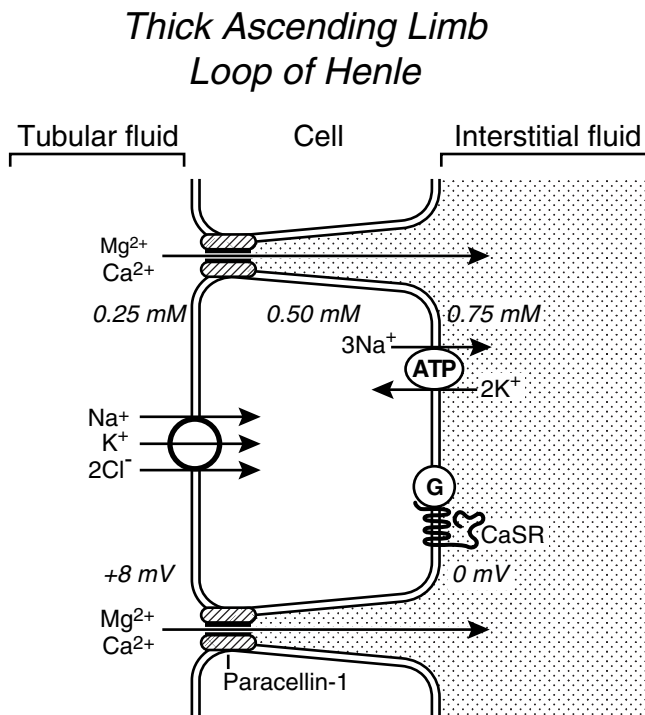
Approximately 80% of total serum magnesium is filtered by the glomerulus and enters the proximal tubule. Studies in numerous mammalian species have documented that approximately 10% to 15% of magnesium is reabsorbed within the proximal tubule.<sup>116</sup> This

is in sharp contrast to most other major cations, for which at least 60% of reabsorption occurs in the proximal tubule. The reabsorption process in this segment of the nephron appears to occur via passive and unsaturable mechanisms and is unchanged by numerous other factors that play a role in other nephron segments. Based on available data, absorption of magnesium in this tubular segment appears to occur through paracellular transport, but the precise mechanism is not known.

### Loop of Henle

The loop of Henle is the site of the majority of magnesium absorption from the kidney. Approximately 60% to 70% of filtered magnesium is reabsorbed in the cortical thick ascending limb of the loop of Henle.<sup>116,137</sup> The medullary thick ascending limb does not appear to participate in magnesium balance.<sup>143</sup> Evidence gathered to date indicates that magnesium absorption in this segment occurs via the paracellular pathway through tight junctions between renal epithelial cells. Numerous factors may influence the transport of magnesium (Fig. 8-2). The principal force allowing magnesium transport in the loop, as in the gut, appears to be the electropositive luminal environment created by the movement of sodium and chloride from the lumen to the interstitial space.<sup>116</sup> In addition, magnesium movement through the tight junctions occurs as a result of “solvent drag” created by the salt and water movement. The positive intraluminal charge facilitates movement of magnesium (and calcium) from the lumen to the interstitium through a paracellular “pore” or channel. Recently, a tight junction protein called PCLN-1 or claudin-16 was discovered that is now thought to be the primary divalent cation channel permitting paracellular movement of magnesium and calcium in the thick ascending limb.<sup>17,31,137,146</sup> A study in humans with inherited defects in this protein has demonstrated significant impairment of magnesium and calcium reabsorption in the thick ascending limb with no change in sodium and chloride reabsorption.<sup>17</sup> A similar genetic anomaly has been documented in Japanese Black cattle that develop early renal failure.<sup>66,105,135</sup> When compared with each other, renal handling of magnesium and calcium appears to be similar in both the bovine and human conditions.<sup>106</sup>

Changes in the transepithelial voltage and paracellular permeability to magnesium strongly influence magnesium absorption from the thick ascending limb.<sup>31</sup> Increases in salt movement from the lumen will concurrently elevate the transepithelial electrical potential and facilitate magnesium absorption. Numerous factors can influence both of these properties, resulting in an increase or decrease in magnesium absorption. Hormones such as PTH, calcitonin, glucagon, antidiuretic hormone, aldosterone, and insulin all act to increase magnesium absorption from the lumen.<sup>31</sup> Conversely,



**Fig. 8-2** Magnesium transport in the cortical thick ascending limb of the loop of Henle. Magnesium transport occurs exclusively through paracellular tight junction cation pore paracellin-1. Transport of magnesium through paracellin-1 down a favorable electrical gradient is enhanced by net reabsorption of sodium and water and the influence of cation-sensing receptor (CaSR).

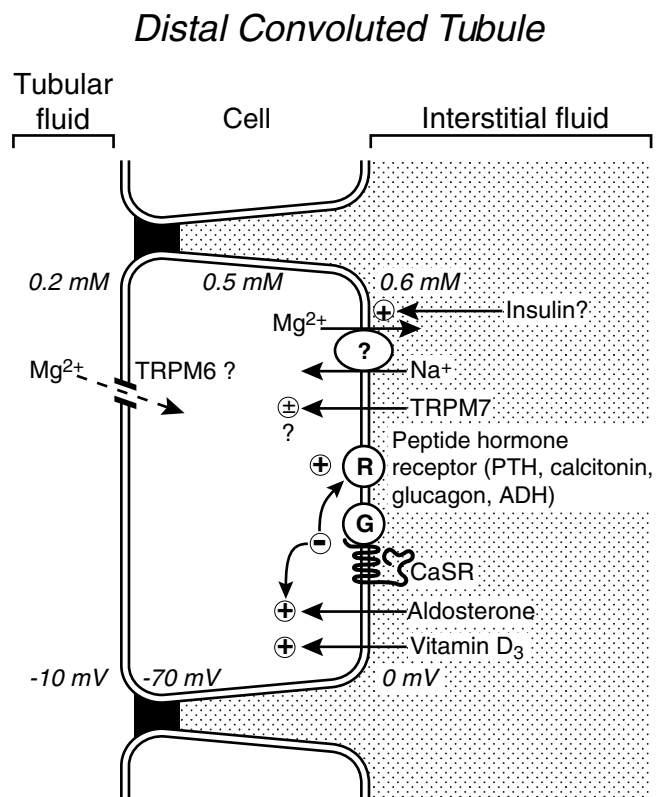
prostaglandin  $E_2$ , hypokalemia, hypophosphatemia, and acidosis can all act to decrease magnesium absorption.<sup>31</sup>

In addition to the above influences on paracellular absorption of magnesium, a basolateral extracellular receptor, termed the calcium/magnesium sensing receptor or cation-sensing receptor (CaSR), also appears to play a crucial role.<sup>31,143</sup> The CaSR senses extracellular calcium and magnesium concentrations at the basolateral membrane and is coupled to intracellular inhibitory G proteins, which will inhibit and neutralize the effect of other hormonal influences mentioned above.<sup>31,33,143</sup> Activation of the CaSR in the loop appears to decrease salt absorption (sodium, magnesium, and calcium).<sup>33</sup> To what effect, if any, the CaSR may play a role in altering the permeability of PCLN-1 to magnesium transport is not known. Some researchers have suspected that there is a selective effect on paracellular permeability to magnesium that cannot adequately be explained by changes in voltage and hormonal influences, leading to speculation that the CaSR may influence PCLN-1 permeability.<sup>34</sup> The CaSR is also found throughout the gut, and although its function there, related to magnesium balance, is not completely understood, it likely plays a very similar role in both organs.<sup>75</sup>

## Distal Convolved Tubule

The distal convoluted tubule (DCT) does not appear to act as a mass transporter of magnesium as the ascending loop does, but instead it is the site for many complex influences to determine the final magnesium excretion (Fig. 8-3). The DCT normally reabsorbs approximately 10% to 15% of the filtered magnesium.<sup>33,143</sup> When necessary it can be very efficient at reabsorbing magnesium, reabsorbing as much as 70% to 80% of the magnesium that is delivered from the thick ascending limb.<sup>33,143</sup> There does not appear to be any ability to further reabsorb or secrete magnesium in nephron segments distal to the DCT; thus the final concentration of magnesium in the urine is principally determined by the DCT.

Reabsorption of magnesium in the DCT appears to occur only through active transcellular routes. Passive paracellular transport does not appear to occur to any sig-



**Fig. 8-3** Magnesium transport in the distal convoluted tubule. Magnesium transport occurs exclusively via transcellular mechanisms down a favorable electrical gradient and is postulated to occur through TRPM6 ion channels. Basolateral movement of magnesium is postulated to occur via a sodium-magnesium transporter. Several peptide hormones exert a positive influence on magnesium reabsorption by binding to a peptide hormone receptor (PTH, parathyroid hormone; ADH, antidiuretic hormone) or via non-receptor-mediated mechanisms. The cation-sensing receptor (CaSR) has a net negative influence on magnesium reabsorption by inhibiting the positive effects of other hormones. TRPM7 ion channels may be involved in basolateral magnesium sensing by the cell.

nificant degree. As a result, the absorption of magnesium via this route is an energy-requiring saturable process. The transcellular transport of magnesium is dependent on favorable transepithelial concentration and voltage gradients, similar to the gut.<sup>33</sup> Mounting evidence suggests that the principal entry for magnesium into the cell is through the unique transient receptor proteins, TRPM6 and TRPM7.<sup>31,33,80,99</sup> One research group has further speculated that TRPM6 is the principal apical or luminal receptor protein facilitating transport of magnesium from the environment to the ECF, and that TRPM7's role is less well defined, perhaps functioning more as an extracellular sensing mechanism that provides feedback to the cell.<sup>139</sup> The unique protein kinase activity that these ion channels possess suggests that their role in the cell is complex and serves some regulatory process.

Although evidence that influx of magnesium into the cell via TRPM6 (and possibly TRPM7) is mounting, there is not yet a documented mechanism of magnesium efflux from the basolateral cell membrane. Based on available evidence, several authors speculate that a sodium/magnesium countertransporter is likely to exist.<sup>33,143</sup> The presence of a sodium/magnesium countertransporter appears to exist in human red blood cells, and insulin appears to be at least one of the regulating influences on its function.<sup>51</sup>

Although the precise mechanisms for magnesium entry and exit from the DCT cells remain to be completely identified and described, the influence of other factors on magnesium transport in DCT cells has been more completely studied. Through complex intracellular signaling pathways, numerous hormones play a role in regulating magnesium transport. PTH, glucagon, anti-diuretic hormone, insulin, aldosterone, 1,25-dihydroxy-cholecalciferol, prostaglandin E<sub>2</sub>,  $\beta$ -adrenergic agonists, and increased sympathetic stimulation via the renal nerve have all been shown to play a role in increasing magnesium conservation.<sup>33</sup> The intracellular signaling pathways that occur following activation of the receptor by any of these hormones/factors are complex and interrelated. As a result, the role of each individual factor, particularly amid the "noise" of multiple simultaneous influences, is difficult to predict. Regardless, however, the sheer number of regulatory signals being sent to this portion of the nephron underscores the importance of magnesium balance within the organism.

Like the gut and the thick ascending limb, the DCT also possesses significant concentrations of the CaSR. Further study of this receptor suggests that there may be the potential for separate binding sites for both calcium and magnesium.<sup>33</sup> Thus the receptor may be able to sense the extracellular concentrations of both ions and send independent signals to intracellular regulators, allowing for completely separate control of magnesium and calcium balance. Once activated with magnesium, however, the CaSR sends a strong inhibitory signal via G

proteins, which negate the positive influence of peptide and steroid hormones and vitamin D<sub>3</sub> on magnesium transport.<sup>33</sup> How it accomplishes this is not yet clear. Possible sites of action include the purported basolateral sodium/magnesium countertransporter or gating of the TRPM6 or TRPM7 ion channels.<sup>33</sup>

The influence of other electrolyte and acid-base abnormalities also can exert a powerful negative effect on magnesium transport in the DCT. As in the loop of Henle, hypokalemia, hypophosphatemia, and acidosis all decrease magnesium reabsorption.<sup>33</sup> The precise mechanism of how these factors influence magnesium transport is not known, and it is likely that each has a different mechanism. Therefore their combined effect can be additive because they influence magnesium transport in different ways.

### EFFECTS OF LACTATION

The nutrient composition of both dog and cat milk has been recently studied.<sup>1,2</sup> Magnesium content of both cat and dog milk appears to be modestly higher during the first 2 to 3 days of lactation, or in the colostrum of both of these species, and then tends to remain at a constant level throughout the remainder of the lactation period.<sup>1,2</sup> This is in sharp contrast to calcium levels that increase consistently throughout the lactation.<sup>1,2</sup>

The contrasting presentation of postparturient hypocalcemia among species is an area that has not been completely explained and is thus an area in which further study is needed. The classic tetanic presentation of postparturient hypocalcemia in dogs is markedly different from the paretic presentation of cattle. In addition, the tetanic presentation of hypomagnesemia or "grass tetany" in cattle adds further evidence to suggest that neuromuscular transmission is affected by complex interactions between calcium and magnesium. A case report of a lactating bitch with significant hypocalcemia and hypomagnesemia that presented with paresis rather than tetany adds to the speculation that the type of presentation is dependent on numerous electrolyte factors and interactions among them.<sup>8</sup> A follow-up retrospective study of serum electrolyte concentrations in 27 bitches with eclampsia or postparturient hypocalcemia revealed that 12 (44%) were concurrently hypomagnesemic, further suggesting that magnesium concentrations may play a role in the pathophysiology of eclampsia in the dog and that magnesium concentrations should be assessed in bitches with eclampsia.<sup>9</sup>

Undoubtedly, lactation does play a role in gut and renal handling of magnesium. Elevation of PTH, in addition to calcium concentration, most likely plays a role in magnesium conservation during lactation to supply the mammary glands with sufficient magnesium. The pathophysiology of calcium and magnesium handling during lactation and the exact triggers that result in eclampsia will require further study.

## MANIFESTATIONS OF MAGNESIUM DEFICIT

A large body of research is present in the scientific literature evaluating the effects of magnesium deficit induced in animal models. Rodent models have been most commonly used, but early literature also evaluated the effects of magnesium-deficient diets in young growing dogs. Several of these early canine studies showed dramatic changes that occurred within 2 weeks of introduction of the diet with increasing severity until 5 to 7 weeks when the animals were euthanized.<sup>13,22,23,111,157</sup> Poor growth rates and numerous dermatological and soft tissue problems, such as dry brittle hair and nails, peripheral vasodilation, and swelling and splaying of the paws, were identified in the early weeks of these trials. After 5 to 7 weeks, however, neuromuscular signs including seizure activity were noted and were postulated to contribute to the death of these animals.<sup>111,157</sup> In two studies, significant myocardial necrosis with associated fibrosis and calcification was also noted after euthanasia.<sup>149,164</sup> Results of these trials assisted researchers in understanding magnesium's physiologic role in the organism. As technology has improved, so too has our understanding of the central role magnesium plays in the maintenance of healthy organisms.

Magnesium's importance to living organisms can be traced through early development of life.<sup>3</sup> Primeval oceans contained large quantities of magnesium, and the earth's crust at the time was predominantly composed of iron-magnesium silicate. As early plants perfected photosynthesis, magnesium played a core role in energy production as a component of chlorophyll. As animal life developed, magnesium played another core role in the production of ATP. In fact, as life has developed on earth, magnesium and calcium appear to have played complementary roles to each other, with magnesium being involved in energy production and cell metabolism, and calcium's role defined more by the essential role it plays in structural stability (bone) and movement (neuromuscular activity). Magnesium's evolution as a "behind-the-scenes" ion that keeps the inner machinery of the cell running smoothly and supplied with ample amounts of energy has perhaps contributed to the long period in which it received little clinical attention. However, this electrolyte recently has been placed under greater scrutiny, and it has been the focus of clinical research activity.

Magnesium plays a pivotal role in many cellular metabolic processes. Although magnesium is the second most abundant intracellular cation, most of the intracellular magnesium is bound to numerous molecules that regulate energy production, storage, and utilization.<sup>4</sup> Magnesium plays a vital role in the mitochondria during oxidative phosphorylation and anaerobic metabolism of glucose.<sup>4</sup> In addition, magnesium participates in a num-

ber of other important intracellular events, such as the synthesis and degradation of DNA, the binding of ribosomes to RNA, adenine nucleotide synthesis, and the production of important intracellular second messengers like cyclic adenosine monophosphate (cAMP).<sup>4,112</sup> Perhaps most well known is magnesium's function as a cofactor with ATP as the driving force behind intracellular ion pumping activity. Significant ion pumps such as the membrane-bound  $\text{Na}^+, \text{K}^+$ -ATPase,  $\text{HCO}_3^-$ -ATPase, and  $\text{Ca}^{2+}$ -ATPase all require  $\text{Mg}^{2+}$ -ATP to maintain effective ionic gradients within and outside the cell.<sup>4,94</sup> As a result, magnesium has an important function in maintaining appropriate intracellular potassium concentrations and serves to regulate cytoplasmic calcium concentrations by stimulating the sequestration of calcium into the endoplasmic and sarcoplasmic reticula. The importance of magnesium's intracellular role becomes apparent clinically in several conditions.

### CARDIOVASCULAR SYSTEM

Contraction of both cardiac and smooth muscle is a complex sequence of events that is orchestrated by many factors and requires rapid shifting of intracellular ions to maintain appropriate concentration gradients. Intracellular calcium, released from the sarcoplasmic reticulum or entering the cell from the extracellular space, is the initiating factor in muscle contraction. Magnesium (both intracellular ionized magnesium level and extracellular level) plays an important regulatory role in the intracellular cycling of calcium in muscle cells. It is a cofactor for the  $\text{Ca}^{2+}$ -ATPase that rapidly shunts intracellular calcium back into the sarcoplasmic reticulum after the contraction cycle is complete. In addition, there is some evidence to suggest that extracellular magnesium may act as a calcium channel blocker for some cell membrane-bound calcium channels, limiting the influx of extracellular calcium into the cytosol.<sup>71,94</sup> Intracellular and extracellular magnesium levels thus play an important role in cardiac excitability, contraction, and conduction through their regulatory effects on calcium movement.

Cardiac conduction electrophysiology is complex and involves finely orchestrated movement of sodium and calcium ions into and of potassium out of the myocytes to propagate an action potential and depolarize the cell. Rapid restoration of those electrolytes against their normal electrochemical gradients occurs to allow the cell to repolarize itself and prepare for the next action potential to occur. Magnesium has several roles in this process. First, magnesium is a cofactor for the ionic pumps that rapidly pump sodium out of the cell, potassium back into the cell, and calcium out of the cell or back into the sarcoplasmic reticulum. In addition, magnesium serves as an important gating mechanism to control the movement of intracellular calcium as described above, and it also acts to prevent leaking of potassium from inside the cell. Intracellular calcium overload triggered during

myocardial ischemia by mediators such as lysophosphatidyl choline (LPC) has been implicated as an important cause of ventricular arrhythmias that result from ischemic conditions.<sup>115</sup> Magnesium may act as an antiarrhythmic agent by limiting intracellular calcium overload in such conditions.<sup>115</sup>

Cardiac arrhythmias are clinical manifestations that can arise from derangements of intracellular or extracellular electrolyte concentrations of magnesium, potassium, and calcium.<sup>70,122</sup> Common arrhythmias documented in humans in which magnesium deficit has been implicated as a cause of, or contributing to the severity of, include atrial fibrillation, supraventricular tachycardia, torsade de pointes, ventricular ectopy, ventricular tachycardias, and toxic digitalis arrhythmias.<sup>119,130,166</sup> Some but not all of these arrhythmias may have an association with hypomagnesemia in veterinary patients, but no definitive studies have documented the prevalence of various pathophysiological causes of arrhythmias in veterinary patients.

Magnesium's effect on the peripheral vasculature is also significant. Magnesium appears to control or exert a powerful role in calcium cycling in the smooth muscle of the peripheral vasculature, with higher intracellular concentrations of magnesium producing a relaxing or vasodilating effect.<sup>84,94,140</sup> Low concentrations of intracellular magnesium appear to have the opposite or vasoconstricting effect. As a result, magnesium deficit has been implicated as a potential contributing cause in the constellation of causes of systemic hypertension.<sup>84,140</sup> The recent discovery of TRPM6 and TRPM7 channels in vascular smooth muscle cells further implicates the important role magnesium has to play in the complex control of vascular smooth muscle.<sup>153</sup> Research has also shown that magnesium plays an interesting role in the production of inflammatory cytokines and reactive oxygen species that have been postulated to play an important role in many common diseases of the cardiovascular system of humans.<sup>84,140,160-163</sup> The origin of this research interest was the cardiac necrosis and lesions in the myocytes of animal models fed magnesium-deficient diets.<sup>161</sup> The cause of these lesions and cardiac dysfunction appears to be reactive oxygen species that originate from neuropeptide substance P-induced activation of macrophages, neutrophils, and mast cells and an increase in important up-regulating inflammatory cytokines such as tumor necrosis factor  $\alpha$  and interleukin-1.<sup>160-163</sup> A study investigating a potential link between feline cardiomyopathy and magnesium status has been reported.<sup>55</sup> It was not successful in showing any link between magnesium and feline hypertrophic cardiomyopathy but included only a small number of cats and did not robustly evaluate magnesium status. Animal models evaluating cardiac effects of magnesium deficit have also shown an increased susceptibility to ischemic and reperfusion injury, indicating that magnesium also has a protective antioxidant effect.<sup>94,163</sup>

The effect of magnesium on the electrocardiogram of dogs fed magnesium-deficient diets has been reported several times with very conflicting results.<sup>109,149,164</sup> One study reported a concurrently developing hypokalemia with an increase in peaked T waves and slight depression of the ST segment in addition to various arrhythmias.<sup>109</sup> A second study reported a decrease in the PQ and QRS distances and an increased incidence of negative T waves but did not evaluate concurrent electrolyte disturbances.<sup>149</sup> A third study reported yet another set of findings that included an increased incidence of mild hypocalcemia but normokalemia and transient RST segment and T wave changes that were not consistent or frequent enough to allow the authors to make any definitive conclusions about electrocardiographic changes associated with hypomagnesemia.<sup>164</sup>

### NEUROMUSCULAR SYSTEM

The role of magnesium in neuromuscular transmission is important as evidenced by the severe clinical signs that may manifest in deficient states. Currently, our understanding of the precise role of magnesium in neuromuscular transmission is limited. In general, magnesium depletion leads to an increased neuronal excitability and enhanced neuromuscular transmission, with the opposite effects predominating in states of magnesium excess.

In small animal patients, neuromuscular signs of hypomagnesemia are rare. Perhaps the most instructive example of acute central nervous system magnesium deficit is "grass tetany" or "grass staggers" of cattle. In this condition, increased neuronal hyperexcitability and neuromuscular transmission occur, causing severe muscle tetany and seizure activity that frequently results in death. Chronic forms of magnesium deficit in humans have also been implicated in any number of neurological and neuromuscular conditions, including migraine headache, sudden infant death syndrome, age-related dementias, chronic fatigue syndrome, and many other psychiatric and sleep-related disorders.<sup>42-44,46,47,49</sup> An acute neurological condition similar to grass tetany and suspected to have been caused by magnesium deficit has also been described in a high school football team.<sup>83</sup> The pathophysiology of the acute and chronic clinical forms of magnesium deficit is likely to be multifactorial, but several contributing causes have been postulated. A decrease in neuronal magnesium concentration is thought to increase the likelihood of calcium binding to presynaptic acetylcholine vesicles, increasing release of acetylcholine into the neuromuscular cleft and increasing the likelihood of muscle contractions.<sup>58</sup>

In addition, magnesium has been shown to block *N*-methyl-D-aspartate (NMDA) receptors within the central nervous system. NMDA receptors are involved in numerous central nervous system functions, including pain sensation and excitatory neurotransmitter activities.<sup>40</sup> Some researchers have also speculated that NMDA receptor

blockade by magnesium may play a role in bronchial smooth muscle relaxation.<sup>136</sup> Other causes that have been identified as potential contributing factors to neuromuscular effects of magnesium deficit include increased excitatory neurotransmitter release, decreased inhibitory neurotransmitter release, production of inflammatory neuropeptides (substance P), loss of antioxidant reserves, and the important influence of magnesium on numerous intracellular second messenger systems.<sup>42,44</sup>

### ELECTROLYTE DISTURBANCES

Numerous concurrent electrolyte disturbances have been reported in association with magnesium deficit. Most commonly reported, in several species, and best studied is the depletion of potassium. During a magnesium-deficient state, the simultaneous occurrence of intracellular potassium loss and decreased ability for potassium to reenter the cell leads to a significant intracellular depletion of potassium. In some cases, a refractory state of hypokalemia occurs despite aggressive supplementation with potassium and resolves only when the magnesium deficit has also been corrected.<sup>62,168</sup> Several mechanisms may contribute to hypokalemia. Magnesium's function as a cofactor for most ATPase pumps likely plays a dominant role. Reduced Na,K-ATPase function will lead to a net loss of potassium outside the cell and a net gain of sodium in the cell.<sup>168</sup> In addition, a magnesium deficit also decreases the function of the Na-K-Cl cotransport system, thus decreasing potassium reentry into the cell.<sup>53,168</sup> Evidence also suggests that the concentration of Na-K pumps decreases in the cell membrane in response to intracellular potassium depletion that further compounds potassium reentry into the cell.<sup>39</sup> Finally, magnesium appears to act from both within and outside the cell to prevent potassium leak from the cell through potassium channels and other mechanisms that are less well understood.<sup>168</sup> Overall, magnesium acts to maintain appropriate intracellular potassium stores. In the kidney, where significant potassium reabsorption occurs through Na,K-ATPase activity and Na-K-Cl cotransport, magnesium stimulates and permits normal reabsorption to occur. Therefore depletion of magnesium has a permissive effect on intracellular loss, leading to extracellular accumulation of potassium, which is subsequently lost from the body because of ineffective potassium reabsorption mechanisms in the kidney. Frequently, this potassium deficiency is refractory to normal supplementation efforts until the magnesium deficit has also been corrected.<sup>62,168</sup>

Further complicating the relationship between potassium and magnesium is the influence of potassium on magnesium reabsorption in the kidney. In the distal collecting tubule, hypokalemia has been shown to decrease magnesium reabsorption concurrently.<sup>33</sup> Although the amount of magnesium reabsorbed in this

segment of the nephron is not large, it may play a significant role. Thus it appears that potassium and magnesium have a complex interaction in which each assists in the regulation and control of the other. Therefore deficits of one ion often lead to deficits in the other, and an inciting causal factor may be difficult to find in many situations.

Hypocalcemia is also frequently reported as a concurrent electrolyte abnormality in humans with a magnesium deficit. The role of magnesium in regulating intracellular calcium flux is complex. It is not yet known whether a magnesium deficit contributes to net loss of calcium from the intracellular environment. The most likely origin of the concurrent deficiency of calcium and magnesium is loss through the kidney combined with decreased liberation from bone stores. Because magnesium and calcium are the most important divalent cations in the body, reabsorption of these ions, not surprisingly, occurs via similar pathways in the kidney. The influence of multiple hormones, the CaSR and a shared PCLN-1 passive transport pore, is likely to result in similar overall net patterns of loss or gain of divalent cations. In addition, there is some evidence in a canine model to suggest that chronic magnesium deficit impairs the skeletal response to PTH and may decrease the parathyroid gland function.<sup>56,86</sup> In humans, a severe magnesium deficit is thought to result in impaired release and impaired activity of PTH. Magnesium's role as a cofactor in the production of the intracellular signaling molecule cAMP is thought to be a contributing cause to this state of functional hypoparathyroidism.<sup>6,59,130</sup> Although unrelated to the presence of hypocalcemia, a recent study in a mouse model of bone and mineral metabolism has revealed that dietary magnesium deficit is related to significant impairment of bone growth, decreased osteoblast and increased osteoclast numbers, and significant stimulation of important cytokines of inflammation, suggesting that magnesium has a significant but as yet undocumented role in bone metabolism.<sup>129</sup>

### PATHOGENESIS OF MAGNESIUM DEFICIT

Numerous causes for magnesium deficit have been documented. Most commonly, magnesium deficit occurs in hospitalized ill patients as a result of the combined causes of lack of dietary intake in conjunction with excessive loss through the gastrointestinal tract because of diarrhea or through the kidney because of excessive diuresis. Numerous specific causes have been reported to contribute in human patients as shown in Box 8-1.<sup>37,94,119,166</sup> Causes of magnesium deficit in veterinary patients have not been as well documented or reported, although the general mechanisms of magnesium loss are likely to be common among many species.



**Box 8-1****Causes of Magnesium Deficit<sup>37,94,119,166</sup>****Gastrointestinal**

- Reduced intake/starvation/malnutrition
- Chronic diarrhea
- Gastric suction
- Malabsorption syndromes
- Short bowel syndrome
- Gastric bypass surgery
- Colonic neoplasia
- Familial or inherited

**Renal**

- Diabetes mellitus/diabetic ketoacidosis
- Diuretics (except potassium sparing agents)
- Osmotic agents (including hyperglycemia)
- Intrinsic renal causes of diuresis
  - Postobstructive
  - Polyuric acute failure
  - Hyperaldosteronism
  - Hyperthyroidism
- Renal tubular acidosis
- Concurrent electrolyte disorders
  - Hypokalemia
  - Hypercalcemia/hyperparathyroidism
  - Hypophosphatemia
- Drugs
  - Gentamicin
  - Carbenicillin
  - Ticarcillin
  - Cyclosporin
  - Cisplatin
- Postrenal transplantation
- Familial or inherited

**Miscellaneous**

- Excessive loss from:
  - Lactation
- Redistribution
  - Acute myocardial infarction
  - Acute pancreatitis
  - Insulin
  - Catecholamine excess
- Idiopathic

**PREVALENCE OF MAGNESIUM DEFICIT**

Serum hypomagnesemia is one of the most commonly reported electrolyte disturbances in a human critical care population. Numerous studies have been conducted on several differing critical care populations (pediatric, adult, and elderly), and all have revealed serum hypomagnesemia in 4% to 65% of patients tested.\* Increased

mortality has also been reported in human patients with measurable hypomagnesemia when compared with normomagnesemic control subjects.<sup>126,147</sup> Although debate continues to swirl as to whether a magnesium deficit is a contributing cause to the mortality rate or simply an epiphenomenon of more severely ill patients, it would appear that magnesium deficit is an independent risk factor for mortality in critically ill humans.

Very few studies of the prevalence of hypomagnesemia in small animal veterinary patients have been published. Only three studies of the prevalence of magnesium abnormalities in hospitalized ill dogs and cats have been published. Two prospective studies have reported on dogs and cats that were admitted to a critical care unit.<sup>93,151</sup> In these studies, the point prevalence of hypomagnesemia at admission in dogs was reported to be 54% of 48 dogs, and the period prevalence of hypomagnesemia during hospitalization for 57 cats was reported to be 28%.<sup>93,151</sup> A third retrospective study reported a point prevalence of hypomagnesemia in a group of hospitalized dogs that were not necessarily confined to a critical care unit as 6.1% of 3102 dogs.<sup>76</sup> Abstracts for three additional studies in critically ill dogs and cats report a period prevalence of 33.6% of 70 animals (50 dogs and 20 cats), a point prevalence of 50% of 101 dogs, and a point prevalence of 39% of 65 animals (42 dogs and 23 cats) (Chew, unpublished data).<sup>35,174</sup> Based on these reports, it appears that hypomagnesemia is a very common finding of hospitalized dogs and cats that are admitted to a critical care unit.

However, the reported incidence of concurrent electrolyte abnormalities in these patients does not mirror that found in humans. In dogs, it was common to see concurrent hypokalemia.<sup>35,76,174</sup> However, only one study reported concurrent hypocalcemia in dogs (Chew, unpublished data). Unexpectedly, two studies in dogs reported concurrent abnormalities in sodium.<sup>93,174</sup> In two of the feline studies, hypokalemia and hypocalcemia were reported, but there was not sufficient information available to determine the significance (Chew, unpublished data).<sup>35</sup> In the published feline study, no concurrent association with other electrolyte disturbances was reported.<sup>151</sup> Although several studies reported mortality statistics, it is extremely difficult to interpret these findings without benefit of illness scoring systems (e.g., APACHE II).

Numerous veterinary researchers have also reported their findings of the prevalence of serum hypomagnesemia in specific disease conditions. Prospective studies of gastric dilatation-volvulus syndrome and parvoviral enteritis in dogs reported no significant abnormalities of serum magnesium.<sup>14,90</sup> A prospective study of Cavalier King Charles spaniels with myxomatous mitral valve disease reported significant serum hypomagnesemia in affected dogs.<sup>108</sup> A prospective study of cats with diabetes mellitus or diabetic ketoacidosis (DKA) reported a

\*References 27,92,126,132,156,166.

point prevalence of ionized hypomagnesemia of 62% of diabetic cats and 57% of DKA cats.<sup>104</sup> A prospective study of 14 feline renal transplant patients documented a period prevalence of ionized hypomagnesemia of 94%.<sup>175</sup> Interestingly, concurrent hypocalcemia and hypokalemia were documented in the majority of cats with magnesium deficit in this study. A prospective study of cats with chronic renal failure documented ionized hypomagnesemia, hypercalcemia, and elevated parathyroid levels (Chew, unpublished data). One case report and one case series of five dogs have reported hypomagnesemia and hypocalcemia in dogs with protein-losing enteropathy.<sup>24,77</sup> The significance of these studies cannot be overlooked, and they lend strong support to the central concept that magnesium deficit is common in ill and hospitalized dogs and cats. Currently, there is insufficient evidence to know whether a magnesium deficit contributes to mortality in this population of patients. As a result, we cannot also answer the question of whether treatment with magnesium contributes a significant benefit to survival or outcome.

## DIAGNOSIS OF MAGNESIUM DEFICIT

The diagnosis of a magnesium deficit continues to be controversial. The fact that 99% of the body's magnesium stores are located within cells presents a diagnostic challenge for clinicians hoping to identify depletion of the body's magnesium. Given our currently limited ability to peer inside of cells on a routine basis clinically, it should not be surprising that diagnosis of magnesium deficit is difficult and controversial. Despite the challenges, however, numerous diagnostic methods have emerged in concert with the renewed clinical interest in magnesium during the past 20 years. These efforts can be broadly divided into two separate categories: methods that assess magnesium (ionized and total) in various tissues (including blood), and methods that assess magnesium-handling physiology.

The challenge of choosing a tissue to sample from to detect a magnesium deficit is to choose one that is most often reflective of a true total body deficit of magnesium. Total serum magnesium is the most commonly used method of assessing magnesium status because of the ease of obtaining serum samples from patients and the relative simplicity of and the ability to automate the assay. More recently, the development of technology that allowed measurement of ionized serum magnesium has emerged and is becoming widely available. There is no question that blood forms the main method of magnesium transport from dietary ingestion, urinary retention, and movement of magnesium between intracellular stores. Cellular intake of magnesium occurs when ionized magnesium crosses from the blood through the cell membrane and then is complexed and harnessed

into the intracellular magnesium-dependent activities. Ionized magnesium appears to equilibrate rapidly across the cell membrane; thus extracellular ionized magnesium may be reflective of intracellular stores. However, the larger question is how reflective of a total body magnesium deficit is a blood sample? Total serum magnesium represents 1% of the body's magnesium stores, and ionized serum magnesium represents 0.2% to 0.3% of the total body magnesium stores. The lack of a gold standard test to compare both total serum magnesium and ionized serum magnesium assays contributes to the confusion regarding diagnosis of a magnesium deficit. Although it is attractive because of its simplicity, serum magnesium does not correlate with the diagnosis of a suspected magnesium deficit based on clinical signs, nor does it appear to correlate well with serum ionized magnesium.\*

There may be several factors to consider when interpreting the results of a blood magnesium sample, such as adequate dietary intake of magnesium and the rapidity of loss of magnesium from the patient. Patients who lose magnesium rapidly will tend to draw heavily from the serum magnesium to replace an acute intracellular need and may be more likely to have low total serum or ionized serum magnesium levels. Chronic mild inadequate dietary intake of magnesium may allow sufficient time for compensatory mechanisms to increase gastrointestinal absorption, renal reabsorption, and possibly skeletal liberation of sufficient magnesium to maintain normal serum and total body magnesium.<sup>48,50</sup> When these compensatory mechanisms are active, they may be much more effective in coping with an additional acute loss and allowing normal serum levels to be maintained. Based on these alterations between serum and ionized fractions, one study suggested the use of a ratio between total serum and ionized magnesium as being more helpful.<sup>48</sup> Concurrent hormone activity, albumin concentration, sample handling, and acid-base status of the patient may all play a role in serum magnesium concentration (Chew, unpublished data).<sup>†</sup> In addition, redistribution of magnesium from the serum compartment has been reported to occur in acute pancreatitis and myocardial infarction of humans and thus could also affect the serum magnesium status and add further difficulty in interpretation of serum magnesium levels. Several studies have also called into question the ion-selective probe technology that has been used to measure ionized serum magnesium.<sup>25,32</sup> In combination, these factors add a large degree of uncertainty to the interpretation of blood magnesium levels.

Measurement of magnesium in red blood cells, white blood cells, and muscle tissue has also been investigated

\*References 50,69,78,104,119,175.

†References 48,69,78,89,155,170.

as potential assays that are more reflective of intracellular magnesium stores.<sup>14,50,133,141</sup> Because of the complexity of the assays, none have found common clinical usage. In addition, results have not consistently correlated with the clinical assessment of magnesium deficit.<sup>133,141</sup> Newer technologies that may be able to assess intracellular ionized magnesium concentrations, such as nuclear magnetic resonance spectroscopy and fluorescent intracellular probes, hold much promise because they are noninvasive, can assess magnesium in several different tissues, and they assess intracellular magnesium stores.<sup>88,159</sup> Such technology has not yet found widespread clinical usage but is an important research technology.

Assessment of physiologic magnesium handling has been evaluated in one of two ways: assessment of renal magnesium handling and testing magnesium retention. Both are based on the concept that active renal retention of magnesium during total magnesium deficit should occur. In addition, they assume that renal function and renal magnesium handling are adequate and appropriate to the patient's current status. These assays cannot be used in patients with inadequate renal function or in which some defect of renal magnesium handling may be present. Urinary magnesium excretion (24-hour), urinary magnesium clearance, and urinary fractional excretion of magnesium have all been used as methods of evaluating renal magnesium handling. Patients with a magnesium deficit or who have inadequate dietary intake of magnesium would be expected to retain magnesium to a much more significant degree than normal patients. Although these assays have not been widely tested in clinical patients, they have been used as a helpful tool in assessing patients with inadequate dietary magnesium intake and thus increased renal reabsorptive compensatory mechanisms.<sup>103,148</sup> Many human physicians favor the use of a magnesium retention test when assessing magnesium status of their patients. Several studies have evaluated the use of this test in human patients and found it to correlate well with clinical suspicion of magnesium deficit.<sup>68,131</sup> However, one study suggests that the magnesium retention test assesses loss of magnesium from the exchangeable bone stores, which may not be reflective of total body magnesium deficit.<sup>30</sup> The magnesium loading test has not been standardized in human medicine, and several variations of the test are reported.<sup>121</sup> Although a study of a magnesium loading test has been completed in dogs, the results have not been published.<sup>96</sup>

The diagnosis of magnesium deficit is challenging. Currently, there is no consensus regarding the best assay for diagnosis; there are several new technologies that are very promising but have not reached widespread clinical use; and more questions than answers still exist. From the available veterinary literature, it would appear that both ionized serum magnesium and total serum magnesium may be useful when results are low and are consistent with clinical suspicion of a magnesium deficit. It

must be emphasized that a normal result does not rule out a magnesium deficit. Clinical suspicion must still play an important role. The magnesium retention test holds promise, but no reference interval has been established for veterinary patients, and thus it needs to be evaluated more completely in veterinary species.

## PHARMACOLOGIC USES OF MAGNESIUM

In addition to their use as therapy in patients with magnesium deficit, magnesium salts have been used to treat a number of disparate disease processes in humans. Although their use as a therapeutic agent in many of these conditions remains unproven, rigorous clinical trials have not been performed to validate the use of magnesium. The use of magnesium as prophylaxis for migrainous headache in children, as protection from endotoxin challenge, as management for cardiovascular signs of pheochromocytoma, as an adjunctive analgesic agent, and as an adjunctive means of controlling muscular spasms of tetanus are examples of magnesium use in this category.\* Therapeutic use of magnesium has been more completely studied in several other diseases, but its therapeutic efficacy is still controversial. Diseases such as myocardial infarction, acute severe asthma, hypertension, and diabetes mellitus are examples that fit this category.<sup>†</sup> Finally, several conditions have been well studied, and the efficacy of magnesium in conditions such as eclampsia/preeclampsia and several types of cardiac arrhythmias, such as digitalis toxicity, torsade de pointes, and ventricular ectopy, has been shown.<sup>‡</sup>

In small animal veterinary medicine, there are several conditions that warrant consideration of magnesium as a therapeutic agent. For most dogs and cats being fed a commercial food, a dietary magnesium deficit is not a concern. Most commercial dog and cat foods have abundant magnesium supplementation. Therefore the at-risk population for magnesium deficit is predominantly hospitalized dogs and cats, particularly those who have been anorexic for several days and in whom excessive gastrointestinal or renal loss of magnesium could be occurring (see Box 8-1). Patients meeting such criteria should be evaluated for a magnesium deficit. Documented hypomagnesemia or a magnesium retention test suspected of being abnormal (normal values have not been established in small animal patients) should prompt the clinician to consider magnesium therapy to correct the deficit. Although increased mortality has been reported to occur in humans with a magnesium deficit, therapy with magnesium salts has not been studied to determine whether therapeutic

\*References 10-12,26,40,72,73,79,97,114,134,150,154,158,171-173.

†References 5,7,15,16,38,60,61,91,110,123-125,127,128,136,138,142,145,152,165,167,169,177.

‡References 19,29,40,54,57,70,81,98,107,113,115,118,122,144.

intervention with magnesium in such patients changes the clinical outcome. Patients with refractory hypokalemia or hypocalcemia despite seemingly appropriate supplementation should also be evaluated for a magnesium deficit and treated accordingly if one is detected. Bitches presenting with eclampsia should have their magnesium status evaluated in addition to their calcium status. In addition, there are two kinds of patient populations that are routinely encountered in small animal emergency and critical care medicine that are frequently identified with a magnesium deficit. Patients in heart failure with concurrent ventricular arrhythmias and who are being medicated with loop diuretics and/or digitalis constitute one high-risk group. Significantly better control of arrhythmias such as torsade de pointes, ventricular ectopy, and digitalis toxicity is frequently gained in humans from supplementation with magnesium and potassium and correction of underlying electrolyte disturbances and normalization of the myocyte's electrophysiological state.<sup>70,122</sup> Ventricular arrhythmias resulting from an overload of intracellular calcium induced by ischemia and LPC production may also benefit from magnesium administration.<sup>115</sup> The other high-risk population is patients diagnosed with diabetes mellitus and in particular DKA. In diabetic patients, more rapid correction of electrolyte disturbances should be expected when magnesium is used as an adjunctive therapeutic agent. Improved speed of correction of metabolic and electrolyte disturbances in this condition should result in a decreased length and cost of hospitalization. There is also some evidence from human medicine to suggest that magnesium may improve insulin sensitivity and thus glycemic control in diabetic patients.<sup>18,60,110,124</sup>

Magnesium therapy could also be considered experimental or unproven therapy for conditions such as bronchial asthma, pain, tetanus infections, and neuroprotection and cardioprotection following ischemia, hyperkalemia, sepsis, and hypertension (especially related to pheochromocytoma). Very little research has been conducted in veterinary patients related to magnesium's effect on any of these conditions. Limited research has been conducted in a dog model showing magnesium to have a positive effect on bronchoconstriction and pulmonary hypertension.<sup>67,176</sup> An *in vitro* study of the effects of magnesium on hyperkalemia has also been performed on canine myocardial cells revealing a significant attenuation of the detrimental electrophysiological effects of hyperkalemia.<sup>81</sup> Although none of these results are substantial enough to justify the routine clinical use of magnesium for these conditions at this time, they are significant enough to stimulate further study in these areas. In fact, further research related to the therapeutic use of magnesium in any of the conditions mentioned above could easily be conducted in veterinary patients and could serve as a valuable model for human diseases.

Administration of magnesium in dogs and cats has not been studied sufficiently to determine appropriate dosages

for administration. However, the safety of administration of magnesium salts is great. Doses severalfold outside the normal therapeutic range were required to produce significant adverse effects in an anesthetized healthy dog model of magnesium administration.<sup>102</sup> As a result of its relative safety in patients with normal renal function, clinical use of magnesium should not be discouraged because of the lack of study evaluating appropriate dosing. Patients most likely to present with hypermagnesemia are patients that have an impaired renal ability to excrete or clear magnesium; therefore magnesium should be used with extreme caution in such patients and only after assessing magnesium levels. The published dose range for magnesium in dogs has been extrapolated from human medicine and tested empirically.<sup>36</sup> Parenteral magnesium generally is administered intravenously using either the chloride or sulfate salt, both of which are available commercially in several concentrations. Doses for magnesium supplementation can be found in Table 8-1. A rapid loading dose can be administered over minutes in severe cases or when required in emergency situations. Alternatively, in patients who do not require emergent therapy, the same emergency loading dose can be administered during the first 24 hours, followed by a slower administration on subsequent days. A continuous intravenous infusion is usually given following the loading dose until the patient's dietary intake is sufficient to maintain adequate magnesium levels. Severely depleted animals can be maintained on a fast replacement dose for multiple days. Mildly affected animals can be maintained on a slow replacement dose. Magnesium salt solution concentrations greater than 20% should not be administered. Magnesium salt solutions are not compatible with calcium- or bicarbonate-containing solutions. One human magnesium research group has strongly recommended the use of the chloride versus the sulfate salt, citing a greater risk of toxicity from magnesium sulfate.<sup>41,45</sup> However, widespread clinical use of the magnesium sulfate salt has continued, perhaps because of the lack of evidence in human studies to support the allegation of toxicity.

## MAGNESIUM EXCESS

Hypermagnesemia is much less clinically significant than magnesium deficit in veterinary medicine. In the two prospective prevalence studies of magnesium abnormalities performed on hospitalized veterinary patients, the period prevalence documented for hypermagnesemia in 57 cats was 18%, and the point prevalence documented for hypermagnesemia in 48 dogs was 13%.<sup>93,151</sup> In these patients, renal insufficiency or postrenal azotemia was frequently documented. Because magnesium is predominantly excreted in the urine, it is not surprising that decreased ability to excrete magnesium from the kidney may result in hypermagnesemia. Iatrogenic overdose, either through parenteral administration or through oral supplementation, is another common cause of

**TABLE 8-1** Dose Ranges for Magnesium Salts

		mEq Mg/g of salt	mEq/kg/day	mEq/kg/hr	mg/kg/hr
Rapid replacement	MgSO <sub>4</sub>	8.12	0.75-1.00	0.03-0.04	3.7-4.9
	MgCl <sub>2</sub>	9.25	0.75-1.00	0.03-0.04	3.2-4.3
		<b>mEq Mg/g of salt</b>	<b>mEq/kg/day</b>	<b>mEq/kg/hr</b>	<b>mg/kg/hr</b>
Slow replacement	MgSO <sub>4</sub>	8.12	0.3-0.5	0.013-0.02	1.6-2.5
	MgCl <sub>2</sub>	9.25	0.3-0.5	0.013-0.02	1.4-2.2
		<b>mEq/kg</b>	<b>mg/kg</b>	<b>Duration</b>	
Emergency/loading	MgSO <sub>4</sub>	0.15-0.3	19-37	5 min-1 h (emerg)	
	MgCl <sub>2</sub>	0.15-0.3	16-32	24 h (load)	
		<b>mEq/kg/day</b>			
Oral	Several	1-2			

hypermagnesemia in humans but has not been reported in small animal veterinary patients. It appears, based on these very limited data and the lack of clinical case reports of syndromes of hypermagnesemia in the veterinary literature, that elevation of magnesium rarely occurs to such an extent that it produces clinical symptoms in small animal patients. Symptoms reported in human patients include loss of deep tendon reflexes, impaired respiration caused by weak respiratory musculature, mild to moderate hypotension, and electrophysiological derangements of cardiac conduction and cutaneous flushing.<sup>101</sup>

A study of magnesium administration to anesthetized normal dogs at a rate of 0.12 mEq/kg/min revealed that significant adverse cardiovascular effects were not detected until plasma levels exceeded 12.2 mEq/L, which was achieved after a cumulative infusion of 1 to 2 mEq/kg of magnesium.<sup>102</sup> In this model, dangerous arrhythmias and significant hypotension were detected at cumulative doses of 3.9 mEq/kg.<sup>102</sup> Death occurred when cumulative infusions reached 5.9 to 10.9 mEq/kg.<sup>102</sup> Given currently recommended dosage infusions of magnesium, it would be very unlikely to reach these toxic levels; however, the effect of underlying pathologic states could contribute significantly to signs of toxicity at lower doses. Therefore magnesium administration should be used cautiously with careful attention to blood pressure and electrocardiographic monitoring. In the rare circumstance that significant clinical signs attributable to hypermagnesemia are detected, therapy should first consist of immediate discontinuation of any parenteral magnesium supplementation and initiating saline diuresis and administering loop diuretics. If renal function is impaired, peritoneal dialysis or hemodialysis

may be required. Administration of calcium can be considered to antagonize some of the cardiac effects in patients in whom cardiac arrest has occurred.<sup>95</sup>

## REFERENCES

- Adkins Y, Lepine AJ, Lonnerdal B: Changes in protein and nutrient composition of milk throughout lactation in dogs, *Am J Vet Res* 62:1266, 2001.
- Adkins Y, Zicker SC, Lepine A, et al: Changes in nutrient and protein composition of cat milk during lactation, *Am J Vet Res* 58:370, 1997.
- Aikawa JK: *Magnesium: Its biological significance*, Boca Raton, FL, 1981, CRC Press, Inc.
- Alghamdi SMG, Cameron EC, Sutton RAL: Magnesium deficiency—pathophysiological and clinical overview, *Am J Kidney Dis* 24:737, 1994.
- Alter HJ, Koepsell TD, Hilty WM: Intravenous magnesium as an adjuvant in acute bronchospasm: a meta-analysis, *Ann Emerg Med* 36:191, 2000.
- Anast CS, Winnacker JL, Forte LR: Impaired release of parathyroid hormone in magnesium deficiency, *J Clin Endocrinol Metab* 42:707, 1976.
- Antman EM: Magnesium in acute myocardial infarction: overview of available evidence, *Am Heart J* 132:487, 1996.
- Aroch I, Ohad DG, Baneth G: Paresis and unusual electrocardiographic signs in a severely hypomagnesaemic, hypocalcaemic lactating bitch, *J Small Anim Pract* 39:299, 1998.
- Aroch I, Srebro H, Shpigel NY: Serum electrolyte concentrations in bitches with eclampsia, *Vet Rec* 145:318, 1999.
- Attygalle D, Rodrigo N: Magnesium sulphate for control of spasms in severe tetanus. Can we avoid sedation and artificial ventilation? *Anaesthesia* 52:956, 1997.
- Attygalle D, Rodrigo N: Magnesium sulphate for the control of spasms in severe tetanus, *Anaesthesia* 54:302, 1999.
- Attygalle D, Rodrigo N: Magnesium as first line therapy in the management of tetanus: a prospective study of 40 patients, *Anaesthesia* 57:811, 2002.

13. Barnes BA, Mendelson J: The measurement of exchangeable magnesium in dogs, *Metabolism* 12:184, 1963.
14. Bechuk TN, Hauptman JG, Braselton WE, et al: Intracellular magnesium concentrations in dogs with gastric dilatation-volvulus, *Am J Vet Res* 61:1415, 2000.
15. Bernstein WK, Khastgir T, Khastgir A, et al: Lack of effectiveness of magnesium in chronic stable asthma—a prospective, randomized, double-blind, placebo-controlled, crossover trial in normal subjects and in patients with chronic stable asthma, *Arch Intern Med* 155:271, 1995.
16. Bessmertny O, DiGregorio RV, Cohen H, et al: A randomized clinical trial of nebulized magnesium sulfate in addition to albuterol in the treatment of acute mild-to-moderate asthma exacerbations in adults, *Ann Emerg Med* 39:585, 2002.
17. Blanchard A, Jeunemaitre X, Coudol P, et al: Paracellin-1 is critical for magnesium and calcium reabsorption in the human thick ascending limb of henle, *Kidney Int* 59:2206, 2001.
18. Brown IR, McBain AM, Chalmers J, et al: Sex difference in the relationship of calcium and magnesium excretion to glycaemic control in type 1 diabetes mellitus, *Int J Clin Chem* 283:119, 1999.
19. Brugada P: Magnesium: an antiarrhythmic drug, but only against very specific arrhythmias, *Eur Heart J* 21:1116, 2000.
20. Buffington CA, Chew DJ, Dibartola SP: Lower urinary-tract disease in cats—is diet still a cause? *J Am Vet Med Assoc* 205:1524, 1994.
21. Buffington CA, Rogers QR, Morris JG: Effect of diet on struvite activity product in feline urine, *Am J Vet Res* 51:2025, 1990.
22. Bunce GE, Chiemchaisri Y, Phillips PH: The mineral requirements of the dog IV. Effect of certain dietary and physiologic factors upon the magnesium deficiency syndrome, *J Nutr* 76:23, 1962.
23. Bunce GE, Jenkins KJ, Phillips PH: The mineral requirements of the dog III. The magnesium requirement, *J Nutr* 76:17, 1962.
24. Bush WW, Kimmel SE, Wosar MA, et al: Secondary hypoparathyroidism attributed to hypomagnesemia in a dog with protein-losing enteropathy, *J Am Vet Med Assoc* 219:1732, 2001.
25. Cecco SA, Hristova EN, Rehak NN, et al: Clinically important intermethod differences for physiologically abnormal ionized magnesium results, *Am J Clin Pathol* 108:564, 1997.
26. Ceneviva GD, Thomas NJ, Kees-Folts D: Magnesium sulfate for control of muscle rigidity and spasms and avoidance of mechanical ventilation in pediatric tetanus, *Pediatr Crit Care Med* 4:480, 2003.
27. Chernow B, Bamberger S, Stoiko M, et al: Hypomagnesemia in patients in postoperative intensive care, *Chest* 95:391, 1989.
28. Chow FhC, Dysart I, Hamar DW, et al: Effect of dietary additives on experimentally produced feline urolithiasis, *Feline Pract* 6:51, 1976.
29. Cohen L, Kitzes R: Magnesium-sulfate and digitalis-toxic arrhythmias, *JAMA* 249:2808, 1983.
30. Cohen L, Laor A: Correlation between bone magnesium concentration and magnesium retention in the intravenous magnesium load test, *Magnes Res* 3:271, 1990.
31. Cole DEC, Quamme GA: Inherited disorders of renal magnesium handling, *J Am Soc Nephrol* 11:1937, 2000.
32. Csako G, Rehak NN, Elin RJ: Falsely high ionized magnesium results by an ion-selective electrode method in severe hypomagnesemia, *Eur J Clin Chem Clin Biochem* 35:701, 1997.
33. Dai LJ, Ritchie G, Kerstan D, et al: Magnesium transport in the renal distal convoluted tubule, *Physiol Rev* 81:51, 2001.
34. Desfleurs E, Wittner M, Simeone S, et al: Calcium-sensing receptor: regulation of electrolyte transport in the thick ascending limb of henle's loop, *Kidney Blood Pressure Res* 21:401, 1998.
35. Dhupa N: Serum magnesium abnormalities in a small animal intensive care unit population (abstract), *J Vet Intern Med* 8:157, 1994.
36. Dhupa N: Magnesium therapy. In Bonagura J, editor: *Kirk's current veterinary therapy XII*, Philadelphia, 1995, WB Saunders.
37. Dhupa N, Proulx J: Hypocalcemia and hypomagnesemia, *Vet Clin North Am Small Anim Pract* 28:587, 1998.
38. Dominguez LJ, Barbagallo M, Di Lorenzo G, et al: Bronchial reactivity and intracellular magnesium: a possible mechanism for the bronchodilating effects of magnesium in asthma, *Clin Sci* 95:137, 1998.
39. Dorup I: Effects of K<sup>+</sup>, Mg<sup>2+</sup> deficiency and adrenal steroids on Na<sup>+</sup>, K<sup>+</sup>-pump concentration in skeletal muscle, *Acta Physiol Scand* 156:305, 1996.
40. Dube L, Granry JC: The therapeutic use of magnesium in anesthesiology, intensive care and emergency medicine: a review, *Can J Anaesth* 50:732, 2003.
41. Durlach J, Bac P, Bara M, et al: Is the pharmacological use of intravenous magnesium before preterm cerebroprotective or deleterious for premature infants? Possible importance of the use of magnesium sulphate, *Magnes Res* 11:323, 1998.
42. Durlach J, Bac P, Bara M, et al: Physiopathology of symptomatic and latent forms of central nervous hyperexcitability due to magnesium deficiency: a current general scheme, *Magnes Res* 13:293, 2000.
43. Durlach J, Bac P, Durlach V, et al: Are age-related neurodegenerative diseases linked with various types of magnesium depletion? *Magnes Res* 10:339, 1997.
44. Durlach J, Bac P, Durlach V, et al: Neurotic, neuromuscular and autonomic nervous form of magnesium imbalance, *Magnes Res* 10:169, 1997.
45. Durlach J, Bara M, Theophanides T: A hint on pharmacological and toxicological differences between magnesium chloride and magnesium sulphate, or of scallops and men, *Magnes Res* 9:217, 1996.
46. Durlach J, Pages N, Bac P, et al: Biorhythms and possible central regulation of Mg status, phototherapy, darkness therapy and chronopathological forms of Mg depletion, *Magnes Res* 15:49, 2002.
47. Durlach J, Pages N, Bac P, et al: Chronopathological forms of magnesium depletion with hypofunction or with hyperfunction of the biological clock, *Magnes Res* 15:263, 2002.
48. Durlach J, Pages N, Bac P, et al: Importance of the ratio between ionized and total Mg in serum or plasma: new data on the regulation of Mg status and practical importance of total Mg concentration in the investigation of Mg imbalance, *Magnes Res* 15:203, 2002.
49. Durlach J, Pages N, Bac P, et al: Magnesium deficit and sudden infant death syndrome (SIDS): SIDS due to magnesium deficiency and SIDS due to various forms of magnesium depletion: possible importance of the chronopathological form, *Magnes Res* 15:269, 2002.
50. Elin RJ: Magnesium—the 5th but forgotten electrolyte, *Am J Clin Pathol* 102:616, 1994.
51. Ferreira A, Rivera A, Romero JR: Na<sup>+</sup>/Mg<sup>2+</sup> exchange is functionally coupled to the insulin receptor, *J Cell Physiol* 199:434, 2004.
52. Finco DR, Barsanti JA, Crowell WA: Characterization of magnesium-induced urinary disease in the cat and comparison with feline urologic syndrome, *Am J Vet Res* 46:391, 1985.

53. Flatman PW, Creanor J: Regulation of Na<sup>+</sup>-K<sup>+</sup>-2Cl<sup>-</sup> cotransport by protein phosphorylation in ferret erythrocytes, *J Physiol* 517:699, 1999.
54. Frakes MA, Richardson LE: Magnesium sulfate therapy in certain emergency conditions, *Am J Emerg Med* 15:182, 1997.
55. Freeman L, Brown D, Smith F: Magnesium status and the effect of magnesium supplementation in feline hypertrophic cardiomyopathy, *Can J Vet Res* 61:227, 1997.
56. Freitag JJ, Martin KJ, Conrades MB, et al: Evidence for skeletal resistance to parathyroid hormone in magnesium deficiency. Studies in isolated perfused bone, *J Clin Invest* 64:1238, 1979.
57. Frick M, Darpo B, Ostergren J, et al: The effect of oral magnesium, alone or as an adjuvant to sotalol, after cardioversion in patients with persistent atrial fibrillation, *Eur Heart J* 21:1177, 2000.
58. Ghoneim MM, Long JP: The interaction between magnesium and other neuromuscular blocking agents, *Anesthesiology* 32:23, 1970.
59. Glendinning P, Need AG, Nordin BEC: Hypocalcemia. In Morri H, Nishizawa Y, Massry S, editors: *Calcium in internal medicine*, London, 2002, Springer-Verlag.
60. Guerrero-Romero F, Tamez-Perez HE, Gonzalez-Gonzalez G, et al: Oral magnesium supplementation improves insulin sensitivity in non-diabetic subjects with insulin resistance. A double-blind placebo-controlled randomized trial, *Diabetes Metab* 30:253, 2004.
61. Hagg E, Carlberg BC, Hillorn VS, et al: Magnesium therapy in type 1 diabetes. A double blind study concerning the effects on kidney function and serum lipid levels, *Magnes Res* 12:123, 1999.
62. Hamill-Ruth RJ, McGory R: Magnesium repletion and its effect on potassium homeostasis in critically ill adults: results of a double-blind, randomized, controlled trial, *Crit Care Med* 24:38, 1996.
63. Hardwick LL, Jones MR, Brautbar N, et al: Site and mechanism of intestinal magnesium absorption, *Miner Electr Metab* 16:174, 1990.
64. Hardwick LL, Jones MR, Brautbar N, et al: Magnesium absorption—mechanisms and the influence of vitamin-D, calcium and phosphate, *J Nutr* 121:13, 1991.
65. Hayashi H, Hoshi T: Properties of active magnesium flux across the small-intestine of the guinea-pig, *Jpn J Physiol* 42:561, 1992.
66. Hirano T, Hirotsune S, Sasaki S, et al: A new deletion mutation in bovine claudin-16 (cl-16) deficiency and diagnosis, *Anim Genet* 33:118, 2002.
67. Hirota K, Sato T, Hashimoto Y, et al: Relaxant effect of magnesium and zinc on histamine-induced bronchoconstriction in dogs, *Crit Care Med* 27:1159, 1999.
68. Holm CN, Jepsen JM, Sjogaard G, et al: A magnesium load test in the diagnosis of magnesium deficiency, *Hum Nutr* 41:301, 1987.
69. Huijgen HJ, Sanders R, Cecco SA, et al: Comparison of three commercially available ion-selective electrodes for ionized magnesium determination in serum: a two-center study, *Clin Chem* 44:480, 1998.
70. Iseri LT, Allen BJ, Ginkel ML, et al: Ionic biology and ionic medicine in cardiac arrhythmias with particular reference to magnesium, *Am Heart J* 123:1404, 1992.
71. Iseri LT, French JH: Magnesium—nature's physiologic calcium blocker, *Am Heart J* 108:188, 1984.
72. James MF: Magnesium sulphate for the control of spasms in severe tetanus, *Anaesthesia* 53:605, 1998.
73. James MF, Cronje L: Pheochromocytoma crisis: the use of magnesium sulfate, *Anesth Analg* 99:680, 2004.
74. Karbach U, Rummel W: Cellular and paracellular magnesium transport across the terminal ileum of the rat and its interaction with the calcium transport, *Gastroenterology* 98:985, 1990.
75. Kerstan D, Quamme GA: Intestinal absorption of magnesium. In Morri H, Nishizawa Y, Massry S, editors: *Calcium in internal medicine*, London, 2002, Springer-Verlag.
76. Khanna C, Lund EM, Raffé M, et al: Hypomagnesemia in 188 dogs: a hospital population-based prevalence study, *J Vet Intern Med* 12:304, 1998.
77. Kimmel SE, Waddell LS, Michel KE: Hypomagnesemia and hypocalcemia associated with protein-losing enteropathy in Yorkshire terriers: five cases (1992-1998), *J Am Vet Med Assoc* 217:703, 2000.
78. Koch SM, Warters RD, Mehlhorn U: The simultaneous measurement of ionized and total calcium and ionized and total magnesium in intensive care unit patients, *J Crit Care* 17:203, 2002.
79. Koinig H, Wallner T, Marhofer P, et al: Magnesium sulfate reduces intra- and postoperative analgesic requirements, *Anesth Analg* 87:206, 1998.
80. Konrad M, Schlingmann KP, Gudermann T: Insights into the molecular nature of magnesium homeostasis, *Am J Physiol-Renal Physiol* 286:F599, 2004.
81. Kraft LF, Katholi RE, Woods WT, et al: Attenuation by magnesium of the electrophysiologic effects of hyperkalemia on human and canine heart-cells, *Am J Cardiol* 45:1189, 1980.
82. Krejs GJ, Nicar MJ, Zerwekh JE, et al: Effect of 1,25-dihydroxyvitamin-D3 on calcium and magnesium absorption in the healthy-human jejunum and ileum, *Am J Med* 75:973, 1983.
83. Langley WF, Mann D: Central-nervous-system magnesium-deficiency, *Arch Intern Med* 151:593, 1991.
84. Laurant P, Touyz RM: Physiological and pathophysiological role of magnesium in the cardiovascular system: implications in hypertension, *J Hypertens* 18:1177, 2000.
85. Lekcharoensuk C, Osborne CA, Lulich JP, et al: Association between dietary factors and calcium oxalate and magnesium ammonium phosphate urolithiasis in cats, *J Am Vet Med Assoc* 219:1228, 2001.
86. Levi J, Massry SG, Coburn JW, et al: Hypocalcemia in magnesium-depleted dogs: evidence for reduced responsiveness to parathyroid hormone and relative failure of parathyroid gland function, *Metabolism* 23:323, 1974.
87. Lewis LD, Chow FHC, Taton GF, et al: Effect of various dietary mineral concentrations on the occurrence of feline urolithiasis, *J Am Vet Med Assoc* 172:559, 1978.
88. London RE: Methods for measurement of intracellular magnesium: NMR and fluorescence, *Ann Rev Physiol* 53:241, 1991.
89. Lum G: Clinical utility of magnesium measurement, *Lab Med* 35:106, 2004.
90. Mann FA, Boon GD, Wagner-Mann CC, et al: Ionized and total magnesium concentrations in blood from dogs with naturally acquired parvoviral enteritis, *J Am Vet Med Assoc* 212:1398, 1998.
91. Marik PE, Varon J, Fromm R: The management of acute severe asthma, *J Emerg Med* 23:257, 2002.
92. Martin BJ, Black J, McLelland AS: Hypomagnesemia in elderly hospital admissions—a study of clinical significance, *Q J Med* 78:177, 1991.
93. Martin L, Matteson V, Wingfield W, et al: Abnormalities of serum magnesium in critically ill dogs: incidence and implications, *J Vet Emerg Crit Care* 4:15, 1994.
94. Martin L, Wingfield W, Van Pelt D, et al: Magnesium in the 1990's: implications for veterinary critical care, *J Vet Emerg Crit Care* 3:105, 1993.

95. Martin LG: Hypercalcemia and hypermagnesemia, *Vet Clin North Am Small Anim Pract* 28:565, 1998.
96. Martin LG: Intravenous magnesium loading test as a method of evaluating magnesium status in the dog. In Proceedings of the Fourth International Veterinary Emergency Critical Care Symposium, San Antonio, TX, 1994.
97. McCartney CJL, Sinha A, Katz J: A qualitative systematic review of the role of N-methyl-D-aspartate receptor antagonists in preventive analgesia, *Anesth Analg* 98:1385, 2004.
98. McLean RM: Magnesium and its therapeutic uses—a review, *Am J Med* 96:63, 1994.
99. Montell C: Mg<sup>2+</sup> homeostasis: the Mg(2+)nificant TRMP channels, *Curr Biol* 13:R799, 2003.
100. Nadler MJS, Hermosura MC, Inabe K, et al: LTRPC7 is a mg-atp-regulated divalent cation channel required for cell viability, *Nature* 411:590, 2001.
101. Nakatsuka K, Inaba M, Ishimura I: Hyper- and hypomagnesemia. In Morri H, Nishizawa Y, Massry S, editors: *Calcium in internal medicine*, London, 2002, Springer-Verlag.
102. Nakayama T, Nakayama H, Miyamoto M, et al: Hemodynamic and electrocardiographic effects of magnesium sulfate in healthy dogs, *J Vet Intern Med* 13:485, 1999.
103. Norris CR, Christopher MM, Howard KA, et al: Effect of a magnesium-deficient diet on serum and urine magnesium concentrations in healthy cats, *Am J Vet Res* 60:1159, 1999.
104. Norris CR, Nelson RW, Christopher MM: Serum total and ionized magnesium concentrations and urinary fractional excretion of magnesium in cats with diabetes mellitus and diabetic ketoacidosis, *J Am Vet Med Assoc* 215:1455, 1999.
105. Ohba Y, Kitagawa H, Kitoh K, et al: A deletion of the paracellin-1 gene is responsible for renal tubular dysplasia in cattle, *Genomics* 68:229, 2000.
106. Ohba Y, Kitoh K, Nakamura H, et al: Renal reabsorption of magnesium and calcium by cattle with renal tubular dysplasia, *Vet Rec* 151:384, 2002.
107. Olerich M, Rude R: Should we supplement magnesium in critically ill patients? *New Horiz* 2:186, 1994.
108. Olsen LH, Kristensen AT, Haggstrom J, et al: Increased platelet aggregation response in Cavalier King Charles Spaniels with mitral valve prolapse, *J Vet Intern Med* 15:209, 2001.
109. Ono I: The effect of varying dietary magnesium on the electrocardiogram and blood electrolytes of dogs, *Jpn Circ J* 26:677, 1962.
110. Orchard TJ: Magnesium and type 2 diabetes mellitus, *Arch Intern Med* 159:2119, 1999.
111. Orent ER, Kruse HD, McCollum EV: Studies on magnesium deficiency in animals II. Species variation in symptomatology of magnesium deprivation, *Am J Physiol* 101:454, 1932.
112. Page S, Salem M, Laughlin MR: Intracellular Mg<sup>2+</sup> regulates ADP phosphorylation and adenine nucleotide synthesis in human erythrocytes, *Am J Physiol-Endocrinol Metab* 37:E920, 1998.
113. Perticone F, Adinolfi L, Bonaduce D: Efficacy of magnesium-sulfate in the treatment of torsade-de-pointes, *Am Heart J* 112:847, 1986.
114. Poopalalingam R, Chin EY: Rapid preparation of a patient with pheochromocytoma with labetalol and magnesium sulfate, *Can J Anaesth* 48:876, 2001.
115. Prielipp RC, Butterworth JF 4th, Roberts PR, et al: Magnesium antagonizes the actions of lysophosphatidylcholine (LPC) in myocardial cells: a possible mechanism for its antiarrhythmic effects, *Anesth Analg* 80:1083, 1995.
116. Quamme GA, de Rouffignac C: Epithelial magnesium transport and regulation by the kidney, *Front Biosci* 5:D694, 2000.
117. Quamme GA, Dirks JH: Magnesium metabolism. In Narins RG, editor: *Clinical disorders of fluid and electrolyte metabolism*, New York, 1994, McGraw-Hill, Inc.
118. Rasmussen HS, Thomsen PEB: The electrophysiological effects of intravenous magnesium on human sinus node, atrioventricular node, atrium, and ventricle, *Clin Cardiol* 12:85, 1989.
119. Reinhart RA: Magnesium-metabolism—a review with special reference to the relationship between intracellular content and serum levels, *Arch Intern Med* 148:2415, 1988.
120. Rich LJ, Dysart I, Chow FH, et al: Urethral obstruction in male cats: experimental production by addition of magnesium and phosphate to diet, *Feline Pract* 4:44, 1974.
121. Rob PM, Dick K, Bley N, et al: Can one really measure magnesium deficiency using the short-term magnesium loading test? *J Intern Med* 246:373, 1999.
122. Roden DM: Magnesium treatment of ventricular arrhythmias, *Am J Cardiol* 63:G43, 1989.
123. Rodrigo G, Rodrigo C, Burschtin O: Efficacy of magnesium sulfate in acute adult asthma: a meta-analysis of randomized trials, *Am J Emerg Med* 18:216, 2000.
124. Rodriguez-Moran M, Guerrero-Romero F: Oral magnesium supplementation improves insulin sensitivity and metabolic control in type 2 diabetic subjects—a randomized double-blind controlled trial, *Diabetes Care* 26:1147, 2003.
125. Rowe BH, Bretzlaff JA, Bourdon C, et al: Intravenous magnesium sulfate treatment for acute asthma in the emergency department: a systematic review of the literature, *Ann Emerg Med* 36:181, 2000.
126. Rubeiz GJ, Thillbaharozian M, Hardie D, et al: Association of hypomagnesemia and mortality in acutely ill medical patients, *Crit Care Med* 21:203, 1993.
127. Rubenowitz E, Axelsson G, Rylander R: Magnesium in drinking water and death from acute myocardial infarction, *Am J Epidemiol* 143:456, 1996.
128. Rubenowitz E, Motin I, Axelsson G, et al: Magnesium in drinking water in relation to morbidity and mortality from acute myocardial infarction, *Epidemiology* 11:416, 2000.
129. Rude RK, Gruber HE, Wei LY, et al: Magnesium deficiency: effect on bone and mineral metabolism in the mouse, *Calcif Tissue Int* 72:32, 2003.
130. Rude RK, Singer FR: Magnesium deficiency and excess, *Annu Rev Med* 32:245, 1981.
131. Ryzen E, Elbaum N, Singer FR, et al: Parenteral magnesium tolerance testing in the evaluation of magnesium deficiency, *Magnesium* 4:137, 1985.
132. Ryzen E, Wagers PW, Singer FR, et al: Magnesium-deficiency in a medical ICU population, *Crit Care Med* 13:19, 1985.
133. Sacks GS, Brown RC, Dickerson RN, et al: Mononuclear blood cell magnesium content and serum magnesium concentration in critically ill hypomagnesemic patients after replacement therapy, *Nutrition* 13:303, 1997.
134. Salem M, Kasinski N, Munoz R, et al: Progressive magnesium deficiency increases mortality from endotoxin challenge—protective effects of acute magnesium replacement therapy, *Crit Care Med* 23:108, 1995.
135. Sasaki Y, Kitagawa H, Kitoh K, et al: Pathological changes of renal tubular dysplasia in Japanese black cattle, *Vet Rec* 150:628, 2002.
136. Sato T, Hirota K, Matsuki A, et al: The role of the N-methyl-D-aspartic acid receptor in the relaxant effect of



- ketamine on tracheal smooth muscle, *Anesth Analg* 87:1383, 1998.
137. Satoh J, Romero MF: Mg<sup>2+</sup> transport in the kidney, *Biomaterials* 15:285, 2002.
  138. Schenk P, Vonbank K, Schnack B, et al: Intravenous magnesium sulfate for bronchial hyperreactivity: a randomized, controlled, double-blind study, *Clin Pharmacol Ther* 69:365, 2001.
  139. Schmitz C, Perraud AL, Fleig A, et al: Dual-function ion channel/protein kinases: novel components of vertebrate magnesium regulatory mechanisms, *Pediatr Res* 55:734, 2004.
  140. Seelig MS: Consequences of magnesium deficiency on the enhancement of stress reactions—preventive and therapeutic implications (a review), *J Am Coll Nutr* 13:429, 1994.
  141. Seelig MS, Altura BM: How best to determine magnesium status: a new laboratory test worth trying, *Nutrition* 13:376, 1997.
  142. Seelig MS, Elin RJ, Antman EM: Magnesium in acute myocardial infarction: still an open question, *Can J Cardiol* 14:745, 1998.
  143. Shah GM: Renal handling of magnesium. In Morri H, Nishizawa Y, Massry S, editors: *Calcium in internal medicine*, London, 2002, Springer-Verlag.
  144. Shattock MJ, Hearse DJ, Fry CH: The ionic basis of the antiischemic and antiarrhythmic properties of magnesium in the heart, *J Am Coll Nutr* 6:27, 1987.
  145. Silverman RA, Osborn H, Runge J, et al: IV magnesium sulfate in the treatment of acute severe asthma—a multicenter randomized controlled trial, *Chest* 122:489, 2002.
  146. Simon DB, Lu Y, Choate KA, et al: Paracellin-1, a renal tight junction protein required for paracellular Mg<sup>2+</sup> resorption, *Science* 285:103, 1999.
  147. Soliman HM, Mercan D, Lobo SSM, et al: Development of ionized hypomagnesemia is associated with higher mortality rates, *Crit Care Med* 31:1082, 2003.
  148. Stewart AJ, Hardy J, Kohn CW, et al: Validation of diagnostic tests for determination of magnesium status in horses with reduced magnesium intake, *Am J Vet Res* 65:422, 2004.
  149. Syllm-Rapoport I: Electrocardiographic studies in dogs with experimental magnesium deficiency, *J Pediatr* 60:801, 1962.
  150. Thwaites CL, Farrar JJ: Magnesium sulphate as a first line therapy in the management of tetanus, *Anaesthesia* 58:286, 2003.
  151. Toll J, Erb H, Birnbaum N, et al: Prevalence and incidence of serum magnesium abnormalities in hospitalized cats, *J Vet Intern Med* 16:217-221, 2001.
  152. Tosiello L: Hypomagnesemia and diabetes mellitus—a review of clinical implications, *Arch Intern Med* 156:1143, 1996.
  153. Touyz RM, He Y, Yao G: Presence of functionally active Mg<sup>2+</sup> uptake channels, TRPM6 and TRPM7, in vascular smooth muscle cells from wky and shr-differential regulation by aldosterone and angiotensin, *Am J Hypertens* 17:P389, 2004.
  154. Tramer MR, Schneider J, Marti RA, et al: Role of magnesium sulfate in postoperative analgesia, *Anesthesiology* 84:340, 1996.
  155. Unterer S, Lutz H, Gerber B, et al: Evaluation of an electrolyte analyzer for measurement of ionized calcium and magnesium concentrations in blood, plasma, and serum of dogs, *Am J Vet Res* 65:183, 2004.
  156. Verive MJ, Irazuzta J, Steinhart CM, et al: Evaluating the frequency rate of hypomagnesemia in critically ill pediatric patients by using multiple regression analysis and a computer-based neural network, *Crit Care Med* 28:3534, 2000.
  157. Vitale JJ, Hellerstein EE, Nakamura M: Effects of magnesium-deficient diet upon puppies, *Circ Res* 9:387, 1961.
  158. Wang F, Van den Eeden SK, Ackerson LM, et al: Oral magnesium oxide prophylaxis of frequent migrainous headache in children: a randomized, double-blind, placebo-controlled trial, *Headache* 43:601, 2003.
  159. Wary C, Brillault-Salvat C, Bloch G, et al: Effect of chronic magnesium supplementation on magnesium distribution in healthy volunteers evaluated by P<sup>31</sup>-NMRS and ion selective electrodes, *Br J Clin Pharmacol* 48:655, 1999.
  160. Weglicki WB, Mak IT: Commentary on magnesium deficiency, substance P receptor up-regulation and NO overproduction, *Magn Res* 9:331, 1996.
  161. Weglicki WB, Mak IT, Kramer JH, et al: Role of free radicals and substance P in magnesium deficiency, *Cardiovasc Res* 31:677, 1996.
  162. Weglicki WB, Phillips TM: Pathobiology of magnesium deficiency—a cytokine neurogenic inflammation hypothesis, *Am J Physiol* 263:R734, 1992.
  163. Weglicki WB, Phillips TM, Mak IT, et al: Cytokines, neuropeptides, and reperfusion injury during magnesium deficiency, *Ann N Y Acad Sci* 723:246, 1994.
  164. Wener J, Pintar K, Simon MA: The effects of prolonged hypomagnesemia on the cardiovascular system in young dogs, *Am Heart J* 67:221, 1964.
  165. Werner HA: Status asthmaticus in children—a review, *Chest* 119:1913, 2001.
  166. Whang R: Magnesium deficiency—pathogenesis, prevalence, and clinical implications, *Am J Med* 82:24, 1987.
  167. Whang R, Sims G: Magnesium and potassium supplementation in the prevention of diabetic vascular disease, *Med Hypotheses* 55:263, 2000.
  168. Whang R, Whang DD, Ryan MP: Refractory potassium repletion—a consequence of magnesium deficiency, *Arch Intern Med* 152:40, 1992.
  169. White J, Campbell R: Magnesium and diabetes: a review, *Ann Pharmacother* 27:775, 1993.
  170. Whyte K, Addis GJ, Whitesmith R, et al: Adrenergic control of plasma magnesium in man, *Clin Sci* 72:135, 1987.
  171. Wilder-Smith CH, Knopfli R, Wilder-Smith OH: Perioperative magnesium infusion and postoperative pain, *Acta Anaesthesiol Scand* 41:1023, 1997.
  172. Wilder-Smith OH, Arendt-Nielsen L, Gaumann D, et al: Sensory changes and pain after abdominal hysterectomy: a comparison of anesthetic supplementation with fentanyl versus magnesium or ketamine, *Anesth Analg* 86:95, 1998.
  173. Williams S: Use of magnesium to treat tetanus, *Br J Anaesth* 88:152, 2002.
  174. Wingfield WE, Matteson VL: Ionized and serum magnesium in normal and critically ill dogs. In Proceedings of the Fifth International Veterinary Emergency Critical Care Symposium, 1996, San Antonio, TX.
  175. Wooldridge JD, Gregory CR: Ionized and total serum magnesium concentrations in feline renal transplant recipients, *Vet Surg* 28:31, 1999.
  176. Yoshioka H, Hirota K, Sato T, et al: Spasmolytic effect of magnesium sulfate on serotonin-induced pulmonary hypertension and bronchoconstriction in dogs, *Acta Anaesthesiol Scand* 45:435, 2001.
  177. Ziegelstein RC, Hilbe JM, French WJ, et al: Magnesium use in the treatment of acute myocardial infarction in the United States (observations from the second national registry of myocardial infarction), *Am J Cardiol* 87:7, 2001.