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# IMPAIRED ABSORPTION OF MAGNESIUM IN THE AETIOLOGY OF GRASS TETANY

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## SUMMARY

Magnesium is absorbed mainly from the reticulo-rumen and there are a number of factors reducing its absorption. The chief of these is the increased potential difference across the rumen epithelium caused by increased intraruminal potassium concentration. A significant amount of magnesium leaves the extracellular fluid each day as saliva. As only a portion of it is reabsorbed the rest is lost through the endogenous faecal excretion of magnesium. Thus, during impaired magnesium absorption, saliva could play an important role in the aetiology of hypomagnesaemia especially during dietary sodium depletion and the resultant increase in the potassium content of the saliva.

KEYWORDS: Magnesium; hypomagnesaemia; rumen; absorption; saliva.

## INTRODUCTION

Grass tetany, the rapid occurrence of clinical hypomagnesaemia in ruminants when changed from winter diets to grazing young, heavily fertilized grass in spring, is of considerable economic importance in the UK. Pregnant and lactating cows are more susceptible to grass tetany because of their increased magnesium requirement.

The skeleton is the major source of magnesium available for mobilization to support its concentration in the extracellular fluid (ECF) during any impairment of its net absorption from the digestive tract (Martens & Rayssiguier, 1980). It was reported that between 0.86–2.3% of the bone magnesium is in equilibrium with the ECF. This represents total amounts of magnesium available to the animal of only 1.8–3.09 g magnesium in the cow and 160–200 mg magnesium in sheep, the latter being equivalent to the daily endogenous faecal magnesium loss in this species (Field, 1960). The older adult is less able to mobilize magnesium from the skeleton during dietary deficiency so that such animals are more susceptible to grass tetany.

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## MAGNESIUM LOSSES FROM THE BODY

*Endogenous faecal*

Magnesium in the faeces is not solely unabsorbed dietary magnesium, since digestive secretions, e.g. salivary, pancreatic, small intestinal and bile juices, may contain a considerable amount of endogenous magnesium. Levels of endogenous faecal loss in sheep vary from 18–358 mg magnesium $day^{-1}$ (Field, 1959; Rook & Storry, 1962; L'Estrange & Axford, 1964; Powley *et al.*, 1977) and in cattle from 1.5–5 mg magnesium $kg^{-1}$ body weight $day^{-1}$ (Rook & Storry, 1962). Thus, endogenous faecal excretion of magnesium is of considerable magnitude in ruminants and may be increased further by the greater flow of saliva stimulated by diets high in roughage (Rook & Storry, 1962; Care, 1967).

*Urine*

It was found that between 1–3 g of magnesium $day^{-1}$ are excreted in the urine of normomagnesaemic cattle over a range of diets in both dry and lactating animals (Jacobson *et al.*, 1972). A fall in plasma magnesium level to the threshold level has been reported to result in almost complete renal magnesium conservation (Storry & Rook, 1963; Wilson, 1964). The minimum range of urinary magnesium concentration indicating adequate dietary intake is 1.5–4.0 mmol $l^{-1}$ (Horber *et al.*, 1979; Alexander, 1985). A virtual absence of urinary magnesium reflects decreased magnesium absorption rate and high risk of grass tetany and thus indicates an urgent need for magnesium supplementation (Sutherland *et al.*, 1986).

*Milk*

A heavily lactating cow could lose 3–4 g of magnesium $day^{-1}$ from the mammary gland, which represents a large proportion of the dietary magnesium absorbed from the gut. Magnesium concentration of milk is relatively constant even under conditions of reduced feed or magnesium intake or during hypomagnesaemia (Rook & Storry, 1962). Thus, the demand by the mammary gland for magnesium may lead to a fall in milk yield before clinical hypomagnesaemia becomes evident.

*Transfer across the placenta*

The flux of magnesium from the ewe to a singleton foetus was reported to be 0.15, 0.64, 0.69 and 0.70 g magnesium $day^{-1}$ at days at 62, 100, 125 and 143 of gestation, respectively, whereas to twin foetuses, this amount was 0.17, 0.58, 0.66 and 0.74 g magnesium $day^{-1}$, respectively, at the same intervals (Grace *et al.*, 1986).

## ABSORPTION OF MAGNESIUM FROM THE ALIMENTARY TRACT

A major factor involved in the pathogenesis of hypomagnesaemia is reduced absorption of magnesium from the gastrointestinal tract. The dietary factors that can affect the net absorption of magnesium do so either by reduction in the concentration of magnesium ions in the rumen liquor or by directly affecting the magnesium transport process.

*Reticulo-rumen*

It is generally believed that most magnesium absorption in the ruminant animal occurs from the fore-stomachs (Tomas & Potter, 1976a; Field & Munro, 1977; Grace, 1983). In recent years, the use of a washed rumen technique involving temporary isolation of the reticulo-rumen of conscious, standing sheep and heifers has confirmed that substantial magnesium absorption does occur from the reticulo-rumen (Martens & Rayssiguier, 1980; Martens, 1983; Care *et al.*, 1984; Beardsworth *et al.*, 1987; Dua, 1992).

*In vitro* studies using isolated preparations of rumen epithelia also show permeability to magnesium (Martens *et al.*, 1978; Martens, 1985; Martens *et al.*, 1987a) and net absorption rates of magnesium.

*Omasum*

The relative importance of the omasum in the absorption of magnesium remains controversial. The omasum has previously been implicated as a major site of magnesium absorption in ruminants (Ben-Ghedalia *et al.*, 1975; Smith & Horn, 1976; Smith & Edrise, 1978). In some experiments (Tomas & Potter, 1976a) using a magnesium infusion technique, no measurable response in plasma magnesium levels was observed when magnesium was infused into the omasum of sheep. *In vitro* studies (Martens & Rayssiguier, 1980) showed that magnesium was absorbed from the omasum only a little less effectively than from the rumen. The omasum is more important in the cow, because its size in the cow relative to the reticulo-rumen, is larger than in the sheep.

*Contribution of the rest of the gut*

Care and van't Klooster (1965) clearly showed that in the sheep the abomasum was not a significant site of net magnesium absorption. Evidence exists for the passive absorption of magnesium from the small intestine of sheep (Stewart & Moodie, 1956; Strachen & Rook, 1975; Field & Munro, 1977) but Axford *et al.* (1975) showed that there was no net absorption of magnesium from the duodenum of sheep *in vivo*. The small intestine appears to be unimportant as an absorption site because a net secretion of magnesium is commonly observed in this region (Axford *et al.*, 1975; Grace, 1983). Some net absorption of magnesium in the large intestine has also been reported by Pfeffer *et al.* (1970) and Grace *et al.* (1974).

## MAGNESIUM ABSORPTION FROM THE RETICULO-RUMEN— THE NATURE OF THE PROCESS

There is a potential difference (PD) between the blood (positive) and rumen contents which is normally of the order of 30 mV (Dobson & Phillipson, 1958; Ferreira *et al.*, 1966; Martens & Rayssiguier, 1980). Significant net transport of magnesium can occur from lumen to blood against the potential difference and in the absence of a concentration gradient (Martens *et al.*, 1978; Martens, 1985). Evidence from studies of absorption of magnesium from the reticulo-rumen has shown that, at normal intraruminal magnesium concentrations, magnesium absorption occurs mainly as a result of an active process which becomes saturable above magnesium concentrations of 4 mmol $l^{-1}$ in sheep (Brown *et al.*, 1978), and 12.5 mmol $l^{-1}$ in cattle (Martens, 1983).

Magnesium ions pass across the rumen epithelium via a transcellular pathway (Martens, 1983). There are two proposed mechanisms for transcellular magnesium absorption: electrogenic and electroneutral. The electrogenic pathway uses the PD of the apical membrane as driving force for the uptake of magnesium whereas the electroneutral pathway for magnesium is PD-independent and magnesium absorption takes place by exchange with two protons (Leonhard *et al.*, 1989).

Both *in vivo* (Gabel *et al.*, 1987) and *in vitro* (Martens *et al.*, 1978) studies proved that the net efflux of magnesium is independent of water efflux so that solvent drag plays no significant role in magnesium absorption from the rumen.

With *in vitro* experiments, it has been observed that the absorption process of magnesium has a requirement for ATP and the $Na^+$-$K^+$-ATPase pump because the addition of ouabain to the ruminal epithelium reduced net magnesium transport by 90% (Martens *et al.*, 1978). Magnesium is only transported if it is free and in the ionized form (Leonhard *et al.*, 1990).

## FACTORS AFFECTING MAGNESIUM ABSORPTION FROM THE RETICULO-RUMEN

### *Magnesium*

The free magnesium concentration normally found in rumen contents is in the range of 2.5–6.0 mmol $l^{-1}$ (Martens *et al.*, 1978), therefore most of the absorption is by an active process (see above). At artificially high luminal concentrations (8.5 mmol $l^{-1}$), further magnesium absorption is mainly passive (Care & van't Klooster, 1965; McLean *et al.*, 1984), which is true for the entire gastrointestinal tract (Stewart & Moodie, 1956). Thus, the incidence of hypomagnesaemia was significantly reduced in ewes grazing a high magnesium pasture (Moseley & Baker, 1991). There is probably no adaptation in the efficiency of magnesium absorption from the reticulo-rumen in response to a fall in the dietary magnesium intake. Also, as expected, active transport of magnesium from the rumen is not influenced by the plasma magnesium concentration (Martens & Stossel, 1988).

### *Potassium*

The widespread use of potassium fertilizers has led to a potassium content of spring pastures frequently above 4% (Sellers & Dobson, 1960). Potassium which is preferentially absorbed from soil by most of the plants competes with magnesium uptake by the plant (Simesen, 1980). A high content of potassium in grass promotes the incidence of hypomagnesaemia by inhibiting magnesium absorption (Kolb, 1985; Martens & Blume, 1986) and thereby increasing the faecal magnesium level (Suttle & Field, 1967; Tomas & Potter, 1976b; Powley *et al.*, 1977; Field & Suttle, 1979; Greene *et al.*, 1983a). The relationship between ruminal potassium concentration and the decrease in magnesium absorption is not linear (Greene *et al.*, 1983b; Martens *et al.*, 1988). With the isolated washed rumen technique it was observed that when the intraruminal potassium concentration was increased from 30 to 110 mmol $l^{-1}$ and sodium concentration decreased from 110 to 30 mmol $l^{-1}$, keeping the magnesium concentration constant at 2.5 mmol $l^{-1}$, there was a 25% decrease in the magnesium absorption rate (Beardsworth *et al.*, 1987; Dua, 1992). In addition, diets with high potassium and low magnesium content have been associated with a decrease in the food intake of animals which would further decrease the magnesium concentration in the rumen (Kunkel *et al.*, 1953; Suttle & Field, 1969). Moreover, a decrease in urinary magnesium excretion rate has been reported following an increase in the dietary potassium content (Suttle & Field, 1967; Field & Suttle, 1979), suggestive of reduced absorption of magnesium.

It has been shown by Tomas and Potter (1976b) and Wylie *et al.* (1985) in sheep and by Greene *et al.* (1983c) in steers that the effect of potassium is confined to the fore-stomachs. A high potassium intake is associated with alterations of three variables within the rumen: (1) increase in potassium concentration; (2) decrease in sodium concentration; and (3) increased in transmural PD (Martens *et al.*, 1987a).

Potassium is absorbed rapidly from the rumen (Ward, 1969; Dua, 1992). It was recently observed that the rumen epithelium possesses potassium channels in the apical and basolateral membranes (Leonhard *et al.*, 1989). Potassium ions, which are taken up into the epithelial cells by the action of $Na^+$-$K^+$ ATPase in the basolateral membrane, would therefore be able to leave the cells via diffusion towards both the luminal and serosal regions when following its chemical gradients (Fig. 1). These potassium movements should contribute to the formation of PDs across both the apical and the basolateral cell membranes (Martens *et al.*, 1991). They further suggested that increasing the intraluminal potassium concentration should therefore not only increase the transepithelial PD as a result of the increased potassium gradient across the epithelial cell, but should also decrease the apical membrane PD because of reduced potassium diffusion from the cytosolic to the luminal side. In fact, it has been shown that the transepithelial PD increases linearly with the logarithm of the intraruminal potassium concentration (Ferreira *et al.*, 1966; Scott, 1966; Martens & Blume, 1986). The apical membrane PD is probably the driving force for the electrogenic uptake of magnesium into the cell. High luminal concentrations of potassium ions will therefore impair overall magnesium absorption in three ways: by enhanced paracellular magnesium flux from serosa to mucosa ($J^{Mg}_{sm}$) and reduced paracellular magnesium flux from mucosa to serosa ($J^{Mg}_{ms}$), both because of an increase in the transepithelial PD; and, thirdly, by a reduced transcellular $J^{Mg}_{ms}$ because of a decrease in the apical membrane PD. Attempts to block the potassium channels with an intraruminal concentration of quinidine of 1 mmol $l^{-1}$ was not found to be an effective method to prevent acute hypomagnesaemia associated with a high potassium intake on highly fertilized pastures (Dua & Care, 1994).

*Sodium*

The sodium content of young spring grass is frequently low (Butler, 1963) and the application of potash fertilizers also reduces the sodium and magnesium content of fresh spring pasture (L'Estrange & Axford, 1964). It was reported by

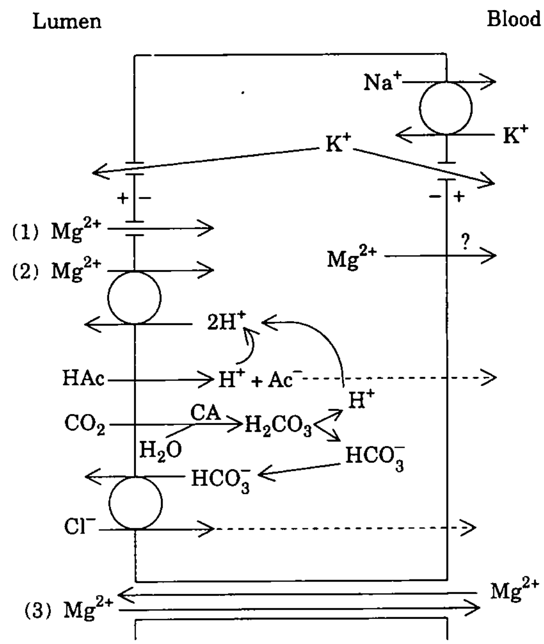


**Fig. 1.** A model of active and passive transport of magnesium ions across ruminal epithelium. (1) Electrogenic transport; (2) electroneutral transport; (3) passive paracellular transport. Ac, acetate; CA, carbonic anhydrase. Adapted from Leonhard (1990).

earlier workers that the availability of magnesium was greater from grass having higher sodium than potassium content (Powley *et al.*, 1977). However, *in vivo* and *in vitro* studies revealed that a change in ruminal sodium concentration did not influence magnesium absorption *per se* (Care *et al.*, 1984; Martens & Blume, 1986; Martens *et al.*, 1987b). However, a low sodium intake caused an increase in the potassium concentrations and a decrease in the sodium concentrations of both saliva and ruminal fluid (Bailey, 1961; Blair-West *et al.*, 1963; Martens *et al.*, 1987b). Thus, a decrease in the Na:K ratio of saliva as a result of increased secretion of aldosterone will further exacerbate the already reduced Na:K ratio of the rumen contents resulting from the high intake of the potassium fertilized grass thereby further reducing the magnesium absorption rate.

### *Calcium*

The major site of calcium absorption in ruminants is proximal to the lower section of the small intestine (Smith, 1969). In fact, a substantial amount of calcium, is absorbed from the reticulo-rumen (Care *et al.*, 1984; Care *et al.*, 1989). A minimum amount of calcium is necessary for the proper functioning of the rumen epithelia because in its absence abnormal electro-physiological changes take place (Dua, 1992). Magnesium and calcium can compete for absorption in the small intestine and rumen of sheep (Care & van't Klooster, 1965; Chicco *et al.*, 1973; Care *et al.*, 1984). An increased dietary calcium level has also been reported to increase the dietary magnesium requirement for cattle (Jacobsen *et al.*, 1972).

*Phosphate*

Hypophosphataemia has also been reported to be associated with clinical hypomagnesaemia. Although earlier workers demonstrated the ability of the rumen epithelium to transport phosphate in both directions (Scarisbrick & Ewer, 1951; Parthasarathy *et al.*, 1952; Wright, 1955) the results varied considerably. Recent evidence has highlighted the role of the rumen as an organ for significant phosphate absorption (Breves *et al.*, 1988; Beardsworth *et al.*, 1989; Care *et al.*, 1989). An increase in the concentration of phosphate in the rumen from 2 mmol $l^{-1}$ (phosphorus deficient diet) to 17 mmol $l^{-1}$ (within the range found normally) increased the net absorption rates of both magnesium and calcium from the rumen (Beardsworth *et al.*, 1989). At a very high rumen phosphate concentration (38 mmol $l^{-1}$), precipitation of quanite ($MgNH_4PO_4.6H_2O$) (Axford *et al.*, 1982), or calcium phosphate (Dua, 1992) may begin to occur resulting in decreased absorption from the rumen.

*Ammonia*

The crude protein intake of ruminants grazing young grass fertilized by nitrogenous fertilizers, was increased by approximately 25–35% (Head & Rook, 1955). As this protein is readily fermentable, it leads to increased intraruminal ammonia concentrations up to 30–70 mmol $l^{-1}$ (Martens & Rayssiguier, 1980). Ammonia absorption from the rumen is linearly related to ruminal ammonia concentration between 3 and 18 mmol $l^{-1}$ (Bodekar *et al.*, 1990a) and is normally detoxified in the liver to urea. The absorption of ammonia is augmented by high ruminal concentrations of short chain fatty acids (SCFA) (Bodekar *et al.*, 1991).

In response to an acute increase of ruminal ammonia concentration, there is a small increase in the PD (Gabel & Martens, 1986; Bodekar *et al.*, 1990b). A transient decrease of magnesium absorption occurs which is corrected in 4–5 days probably due to the adaptation of the rumen epithelium to the high ammonia concentration (Gabel & Martens, 1986). These workers also found that the effect of ammonium ions on magnesium absorption was greater in the bovine than the ovine rumen. Other contributory causes could be decreased ruminal blood flow and increased pH following an increase in ruminal ammonia concentration (Wilcox & Hoff, 1974).

In the rumen of sheep, quanite ($MgNH_4PO_4.6H_2O$) formation is seen to occur at pH 6.2–7.2 with ruminal ammonia concentration in the range of 40 mmol $l^{-1}$ and depresses the available amount of magnesium (Axford *et al.*, 1982). Attempts were made to prevent the effect of increased ammonia concentration by the use of quinidine in *in vitro* studies (Bodekar *et al.*, 1990b) but until its efficacy is proven *in vivo*, its use as a prophylactic measure must be in doubt. It appears that ruminal ammonia may contribute to decreased magnesium absorption under the circumstances which may be encountered during grazing.

*Organic acids and* $CO_2$

Volatile fatty acids (VFA) and $CO_2$ are products of microbial fermentation and have a stimulatory effect on blood flow through the rumen wall (Thorlacius, 1972). Volatile fatty acids provide the energy for the active transport system across the rumen wall (Martens & Rayssiguier, 1980) and increase magnesium absorption (Martens *et al.*, 1988). Reduced production of VFA and $CO_2$ causes an increase in pH which diminishes the soluble magnesium in the rumen fluid (Smith & Horn, 1976; Johnson & Aubrey Jones, 1989) and magnesium absorption (Horn & Smith, 1978).

*Carbohydrates*

Supplementation of grazing dairy cattle with starch/readily available carbohydrates reduced the degree of hypomagnesaemia (Wilson *et al.*, 1969). Similarly, an apparent magnesium absorption of 15% in sheep fed unsupplemented hay, increased to 35–38% in sheep supplemented with degradable carbohydrates (Giduck *et al.*, 1988). The underlying mechanism may involve lower ruminal pH, higher ruminal concentrations of SCFA and lower concentrations of $NH_3^+/NH_4^+$.

*Individual variation*

It has been found for many years that only a small proportion of any flock or herd will suffer clinical hypomagnesaemia (Butler, 1963; Field, 1983). Many factors appear to contribute towards individual susceptibility, e.g. stress, temperament, subnormal food intake, variation in the rumen capacity and absorptive surface area. A genetic factor for magnesium absorption has also been suggested. It has been reported that the breed of sire has an effect on the efficiency of magnesium absorption and the level of urinary magnesium excretion (Field *et al.*, 1986). Some sheep may have a greater than normal component of electroneutral magnesium absorption and thus be less affected by a high ruminal potassium concentration.

## HORMONAL FACTORS

*Parathyroid hormone (PTH) and Vitamin $D_3$*

In grossly hypomagnesaemic animals there is decreased formation and activity of PTH (Anast *et al.*, 1972; Rayssiguier *et al.*, 1977; Rude *et al.*, 1978) with consequent reduction in the circulatory level of calcitriol [$1,25(OH)_2D_3$], the active metabolite of Vitamin D (Rude *et al.*, 1978). Hypomagnesaemia thus causes target organ resistance to the physiological effects of PTH which ultimately results in reduced bone resorption and calcium absorption from the digestive tract mediated either by $1,25(OH)_2D_3$ or by transcaltachia (Nemere & Norman, 1986). Thus hypocalcaemia often accompanies hypomagnesaemia in grass tetany.

*Aldosterone*

A high potassium or low sodium diet taken by grazing ruminants may elicit an aldosterone response. Hyperaldosteronism is associated with a negative magnesium balance (Charlton & Armstrong, 1989), hypomagnesaemia and increased excretion of magnesium in the urine (Scott & Dobson, 1965) and faeces (Care & Ross, 1963; Simesen, 1980) but the interpretation is complicated by increased addition of salivary potassium to the rumen contents. In adrenal insufficiency, the opposite effects occur and serum magnesium concentration is increased. The prolonged oral administration of captopril (an angiotensin I converting enzyme inhibitor) to decrease the endogenous production of angiotensin II, and thus aldosterone, also increased the plasma magnesium concentration. Similarly, the intraruminal administration of the aldosterone receptor blocker, spironolactone (Aldactone, Searle Pharmaceuticals, High Wycombe, Buckinghamshire) increased the magnesium absorption rate in moderately sodium deplete sheep (Dua, 1992). However Martens and Hammer (1981) found no change in the net magnesium absorption from the isolated reticulo-rumen of sheep following intravenous aldosterone fusion, although adrenalectomized sheep, maintained on a basal level of adrenal corticoids would have been a better subject for this infusion. The role of angiotensin II itself in the part played by dietary sodium deficiency in the aetiology of hypomagnesaemia is currently under investigation.

One of the physiological consequences of the increased circulating concentrations of aldosterone is a reduction in the Na:K ratio in the saliva (Blair-West *et al.*, 1963). As the concentrations of these ions in the rumen are closely correlated with their concentrations in the saliva (Bailey, 1961; Morris & Gartner, 1975), a low Na:K ratio in ruminal fluid is observed during sodium deficiency (Scott, 1966). This would decrease magnesium absorption.

## MAGNESIUM SECRETION

The secretion of magnesium into the rumen is paracellular and is approximately 5–11% of the true magnesium absorption rate when there is no concentration gradient across the rumen wall (Martens, 1983). When there is an increased PD due to increased ruminal potassium concentration there was increased secretion and decreased absorption of magnesium (Martens, 1987a).

## SALIVA

The total magnesium concentration in the mixed saliva of sheep varies between 0.20–0.30 mmol $l^{-1}$ (Dua & Care, 1992) and the total amount of saliva secreted by a sheep varies between 10–15 l $day^{-1}$. Thus about 3–4.5 mmol magnesium (about 40% of the total amount of magnesium available in the extracellular fluid) is secreted in the saliva each day. Normally the absorption rate of magnesium is 20%. When the animals are on tetany prone grass and the magnesium absorption is grossly impaired, losing this much magnesium through saliva makes the animal more susceptible to hypomagnesaemic tetany. This is a major reason for ruminants being more susceptible to hypomagnesaemia than monogastric animals.

## CONCLUSIONS

Since the paper of Sjollema (1930) on hypomagnesaemia in cattle, we now have a greater understanding of the pathogenesis of this disease; yet it is still a source of significant economic loss. Now that it is recognized that the major site of net magnesium absorption is the stratified squamous epithelium common to the ruminant fore-stomachs, a great deal is now known as to the mechanism by which intraruminal potassium ions may reduce the active transport of magnesium ions across the tissue. The origin of this potassium is both diet and saliva, thus leading to the conclusions that the dietary intakes of both magnesium and sodium should be supplemented and that the use of potassic fertilizers should be restricted in order to reduce the incidence of grass tetany. However, the phenomenon of individual susceptibility to grass tetany within a dairy herd of similar animals, the so-called indicator cows, still requires a convincing explanation.

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