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HYPOMAGNESEMIA IN YOUNG CALVES AND EFFECTS OF MAGNESIUM REPLETION ON PLASMA AND CSF MINERALS

A Thesis

Presented for the

Master of Science

Degree

The University of Tennessee, Knoxville

Kathryn Anne McKim

August 1983

ACKNOWLEDGMENTS

The author wishes to express her sincere appreciation and gratitude to the following persons:

To Dr. Marvin C. Bell, major professor and thesis advisor, for his sound and sincere advice, inspiration, and educational guidance throughout her graduate program.

To Dr. James K. Miller and Dr. Michael H. Sims for participation in the collection of data, serving on the graduate committee, and reviewing the manuscript.

To Chris Reynolds, Steve Banet, Nancy Ramsey, and Tina Johnson for their assistance and cooperation in the collection and analysis of the data.

To Dr. James B. McLaren and Peggy Hamlett who provided valuable help with the statistical interpretation of the data.

To her close friends and fellow graduate students for their support throughout the period of graduate study.

Finally, gratefully acknowledging the sacrifices and loving support of my parents William S. and Etta M. McKim toward my quest for this degree, and because of this, my dedication of this thesis to them.

ABSTRACT

Young Holstein calves were used as models for lactating beef cows to better understand the etiology of hypomagnesemia. The objectives were to produce hypomagnesemia in the calves and to determine the effects of excess potassium (K) on magnesium (Mg) metabolism. Procedures included evaluating oral repletion of 50 or 100 ml of 30% $MgCl_2 \cdot 6H_2O$ solution on plasma and cerebrospinal fluid (CSF) and collection of tissues 48 hours post dosing for mineral analysis.

The calves were randomly assigned to one of four different diets. Diet one was Mg deficient, diet two was adequate in Mg, diet three was Mg deficient plus supplemental K, and diet four contained adequate Mg plus supplemental K. When calves fed the low Mg diets became sufficiently deficient in Mg, a five day collection period was conducted in which intake, feces, and urine were measured and aliquots were obtained for analyses.

A balance study was conducted consisting of three separate trials in which only 19 of the total 24 calves were utilized due to calf losses. Calves fed Mg deficient, Mg deficient plus supplementak K, and the adequate Mg plus supplemental K diets excreted .009, .010, and .095 g per day of Mg in the urine, respectively compared to .219 g per day of Mg for calves fed the diet adequate in Mg. Concentrations of K in calves fed diets supplemented in K were higher ($P<.05$) for K intake and urinary

excretion. Fecal excretion of K remained unchanged across treatments. There was a higher ($P<.05$) K balance in calves fed the diet adequate in Mg plus supplemental K than calves fed the Mg deficient diet. Calcium (Ca) balances did not differ across treatments.

Repletion data were obtained from 19 of the 24 calves immediately following the balance period. Plasma and CSF samples were obtained at 0, 5, 15, 30, 60, 120, and 180 minutes. Concentrations of Mg in plasma of calves fed the Mg deficient diet increased from a baseline level of .44 mg/dl to .62 mg/dl 180 minutes after repletion with 50 ml of 30% $MgCl_2 \cdot 6H_2O$ solution. Oral Mg solutions had no effect on plasma Mg in calves on other treatments. Concentrations of Mg in CSF decreased ($P<.05$) from a baseline of 1.76 mg/dl to 1.14 mg/dl at 180 minutes after oral dosing with Mg in calves fed the Mg deficient plus supplemental K diet. However CSF Mg remained fairly constant over the 180 minute period in calves on other treatments.

Tissue samples collected included lung, heart, brain, liver, spleen, kidney, skeletal muscle, and rib. Concentrations of Mg in brain, heart, liver, spleen, skeletal muscle, kidney, or lung were not influenced by dietary intakes of Mg or K. There was a reduction of over 30% ($P<.05$) in rib Mg of calves fed no supplemental Mg when compared to calves fed Mg supplemented diets.

TABLE OF CONTENTS

CHAPTER		PAGE
I.	INTRODUCTION.	1
II.	REVIEW OF LITERATURE.	3
	Etiology of Hypomagnesemia	3
	Magnesium Homeostasis.	12
	Factors Affecting Utilization.	30
III.	EXPERIMENTAL PROCEDURE.	41
	General Design	41
	Procedures and Management.	41
	Data Collected	50
	Chemical Analyses.	54
	Statistical Analysis	55
IV.	RESULTS AND DISCUSSION.	57
	Balance Results.	57
	Repletion Results.	65
	Tissue Results	87
V.	SUMMARY	94
LITERATURE CITED		96
VITA		108

LIST OF TABLES

TABLE		PAGE
1.	Composition of Original Basal Diet.	43
2.	Composition of Modified Basal Diet.	45
3.	Experimental Design	47
4.	Mineral Analysis of Diets (mg/g).	48
5.	Calf Losses Due to Dietary Treatment.	51
6.	Distribution of Calves Used for Statistical Analysis of Balance Study	59
7.	Least Square Means of Daily Magnesium Balance in Grams, Calculated From Average Daily Excretion. .	60
8.	Least Square Means of Daily Calcium Balance in Grams, Calculated From Average Daily Excretion	62
9.	Least Square Means of Daily Potassium Balance in Grams, Calculated From Average Daily Excretion	64
10.	Effect of Oral $MgCl_2 \cdot 6H_2O$ Administration on Plasma Mineral Levels of Calf on 11/19/81	66
11.	Effect of Oral $MgCl_2 \cdot 6H_2O$ Administration on Plasma Mineral Levels of Calf on 12/7/83.	68
12.	Distribution of Calves for Statistical Analysis of Tissues.	89
13.	Least Square Means of Organ Minerals in mg/gram Dry Basis	90
14.	Least Square Means of Tissue Minerals in mg/gram Dry Basis	92

LIST OF FIGURES

FIGURE		PAGE
1.	Regression Curves for Plasma Mg in Hypomagnesemic or Normomagnesemic Calves Fed Normal or Excess K After Oral Dosing with 50 ml of 30% $MgCl_2 \cdot 6H_2O$.	70
2.	Regression Curves for Plasma K in Hypomagnesemic or Normomagnesemic Calves Fed Normal or Excess K After Oral Dosing with 50 ml of 30% $MgCl_2 \cdot 6H_2O$.	72
3.	Regression Curves for CSF Mg in Hypomagnesemic or Normomagnesemic Calves Fed Normal or Excess K After Oral Dosing with 50 ml of 30% $MgCl_2 \cdot 6H_2O$.	74
4.	Regression Curves for CSF K in Hypomagnesemic or Normomagnesemic Calves Fed Normal or Excess K After Oral Dosing with 50 ml of 30% $MgCl_2 \cdot 6H_2O$.	75
5.	Comparison of Repletion with 50 or 100 ml of 30% $MgCl_2 \cdot 6H_2O$ on Plasma and CSF Mg of Calves Fed Mg Deficient Diets	76
6.	Comparison of Repletion with 50 or 100 ml of 30% $MgCl_2 \cdot 6H_2O$ on Plasma Mg of Calves Fed Adequate Mg Diets.	77
7.	Comparison of Repletion with 50 or 100 ml of 30% $MgCl_2 \cdot 6H_2O$ on Plasma and CSF Mg Fed Mg Deficient Plus Supplemental K Diets.	79
8.	Comparison of Repletion with 50 or 100 ml of 30% $MgCl_2 \cdot 6H_2O$ on Plasma and CSF Mg of Calves Fed Mg Adequate Plus Supplemental K Diets.	80
9.	Comparison of Repletion with 50 or 100 ml of 30% $MgCl_2 \cdot 6H_2O$ on Plasma and CSF K of Calves Fed Mg Deficient Diets	81
10.	Comparison of Repletion with 50 or 100 ml of 30% $MgCl_2 \cdot 6H_2O$ on Plasma K of Calves Fed Mg Adequate Diets	82
11.	Comparison of Repletion with 50 or 100 ml of 30% $MgCl_2 \cdot 6H_2O$ on Plasma and CSF K of Calves Fed Mg Deficient Plus Supplemental K Diets	84

FIGURE PAGE

12. Comparison of Repletion with 50 or 100 ml of 30% $MgCl_2 \cdot 6H_2O$ on Plasma and CSF K of Calves Fed Mg Adequate Plus Supplemental K Diets. 85

CHAPTER I

INTRODUCTION

Hypomagnesemia, a metabolic disorder that occurs in ruminants which generally appears within the first two weeks after cattle have been put out on lush spring pasture has been associated with low Mg levels in the plasma and CSF. Losses from death of animals and even to a higher extent production losses make grass tetany a disorder of considerable economic importance (Aikawa, 1981; Bell, 1981). Grass tetany is most prevalent in older animals in early lactation; however, cases have been documented in milk fed calves (Crookshank and Sims, 1955; Grunes et al., 1970; Boling et al., 1979). Fontenot (1979) suggested that older animals are perhaps more susceptible to this disorder because their labile Mg reserve found in bone is lower and less available.

Magnesium absorption has been shown to occur in the reticulorumen with net secretion in the small intestine (Tomas and Potter, 1976a; Stevenson and Unsworth, 1978). The mechanism by which Mg absorption occurs is primarily one of active transport due to the potential difference between the lumen of the rumen and blood (Brown et al., 1978). There are many factors which affect the utilization of Mg by altering its absorption. Increases in crude protein, nitrogen (N) fertilization, Ca, phosphorus (P), and to probably the largest extent excess K decrease the availability of Mg to the animal.

Proper functioning of the central nervous system (CNS) is dependent upon CSF which is formed by the choroid plexus. Normal CSF Mg concentrations in cattle are approximately 2.2 $\pm$ .16 mg/dl according to Meyer and Scholz (1972). In recent years a positive correlation has been found between severe hypomagnesemia and lower CSF Mg levels (Meyer and Scholz, 1972; Pauli and Allsop, 1974). There is a risk of tetany when Mg falls below 1.6 mg/100 ml and a level below 1.2 mg/100 ml tetany is likely to occur (Meyer, 1977).

Bones contain about 60% of the total body content of Mg at a concentration of about 90 meg/kg wet weight. Most of the remaining Mg is distributed equally between muscle and nonmuscular soft tissues (Aikawa, 1981). Approximately 1% of the total body content of Mg is extracellular according to Wilson (1964). Numerous data has shown that Mg concentration of the soft tissues does not deplete in hypomagnesemic animals compared to normal animals; however, bone Mg has shown to deplete up to 30% while animals are maintained on a Mg deficient diet (Wilson, 1964; Littledike and Cox, 1979).

Calves seem to make suitable models for studying the etiology of hypomagnesemia. While they may present more problems than sheep, they may be more advantageous since they are the same species most afflicted with the disorder. Therefore, the objectives of this research were to produce hypomagnesemia in calves and to study the effects of excess K on mineral metabolism. Methodology included oral drench repletion with 30% $MgCl_2 \cdot 6H_2O$ solution and tissue collection.

CHAPTER II

REVIEW OF LITERATURE

I. ETIOLOGY OF HYPOMAGNESEMIA

A metabolic disturbance that occurs in ruminants which generally appears within the first two weeks after cattle have been put out in late winter or early spring to graze lush, rapidly growing pasture has been associated with low Mg levels in plasma. This condition was first documented by Sjollema in 1929. It has more commonly been called grass tetany, wheat pasture poisoning, winter tetany, milk tetany associated with calves, lactation tetany, or grass staggers. Grass tetany has been documented to be fatal to as many as 30% of the animals that show clinical signs; therefore, it is a disorder of considerable economic importance (Aikawa, 1981). Not only are the death losses devastating to cattleman, but Bell (1981) indicated that financial losses due to decreased production are even higher in hypomagnesemic cows.

Types

Some researchers have described hypomagnesemia by partitioning the disorder into specific types. Stewart (1954) described three such types as (1) the spring type, a well defined seasonal disease that affects cows with calves in April and May and occurs within a few days of putting the animals out on grass, (2) the winter type, occurring among cattle being fed winter rations in confinement with

silage or hay, and (3) the out-winter type, affecting cattle maintained throughout the winter on sparse pasture occurring in February and March. On the other hand, Wilson (1964) has divided hypomagnesemia into acute or chronic forms and that due to dietary deficiency of Mg as seen in milk fed calves. The acute hypomagnesemia develops a day or two after animals are turned onto lush growing pasture and is frequently accompanied by tetany or convulsions. The chronic form is associated with seasonal hypomagnesemia in which there is a cyclical variation of plasma Mg throughout the year. Plasma Mg may fall without the classically, cold, wet, windy weather associated with this syndrome. The hypomagnesemia seen in calves is essentially associated with a deficient intake of Mg due to milk as opposed to that due to pastures. This partitioning of hypomagnesemia may help to better understand the mechanisms by which it occurs.

Plasma Levels

Values for the concentration of Mg in plasma or serum reported for normal pigs, cattle, sheep, and goats range from about 1.2 to 3.8 mg/dl of Mg. The lower limit of the normal range in cattle is 1.7 mg/dl, a value now known to be of particular physiological significance, since it is closely related to the renal threshold. Values below that can properly be referred to as hypomagnesemia (Rook and Storry, 1962). Grunes et al. (1970) cites Meyer as classifying animals as hypermagnesemic if they had

greater than 3.2 mg/dl of Mg in their serum, normal from 1.8 to 3.2, slightly hypomagnesemic at 1.2 to 1.8, and severely hypomagnesemic with a value less than 1.2 mg/dl of Mg. It has been demonstrated by data collected that under particular conditions, cattle may tolerate extremely low blood serum Mg levels without showing the clinical symptoms of hypomagnesemia. This is in agreement with work conducted by Rook and Storry (1962) in which low serum Mg values of .5 mg/dl or less, were not invariably associated with clinical signs and in general, mature animals appeared to be less sensitive to low values than calves. Wilson (1964) suggested that the majority of healthy animals will have plasma or serum Mg concentrations between 1.7 and 3.0 mg/dl and the symptoms of nervous origin are likely to occur if the concentration falls below 1.0 to 1.2 mg/dl. However, some animals show no symptoms at very low concentrations while others show symptoms above 1.2 mg/dl.

Not only are plasma Mg levels associated with this disorder but many times plasma Ca levels are also affected especially during long periods of chronic low Mg concentrations. Parr (1957) indicated that serum Ca levels of cattle usually lie within a range of 8.5 to 11.5 mg/100 ml with an average value of about 10 mg/100 ml. In the cases of hypomagnesemia, however, a rapid fall to values as low as 6.5 mg/100 ml often occur.

Animals Affected

There is agreement among researchers that some cows are more susceptible to hypomagnesemia than others. This variation is still not well understood. Boling et al. (1979) stated that the condition is most prevalent in lactating beef cows, with the incidence increasing subsequent to the second lactation. Grass tetany occurs in both fall and spring-calving beef cows grazing cool season grasses, however, the syndrome is more prevalent in the late winter or early spring calving female. Underwood was cited by Grunes et al. (1970) as indicating that hypomagnesemic tetany is most common in older milking cows in the first 10 weeks after calving, although it can occur at any stage of lactation, in animals of any age, including suckling calves three to six months of age. In a study conducted on wheat pasture poisoning all cases were observed in cows two years of age or older, who were pregnant, had a calf at side, or both. The time the animal had the attack varied from the fifth month of pregnancy to six or seven months post-partum; however, the condition has been reported in calves and steers (Crookshank and Sims, 1955). Grunes et al. (1970) indicated that the greatest incidence of hypomagnesemic tetany occurred in cows which had their third or fourth calf. Animals that had six calves were 15.2 times as susceptible to tetany as those with only one calf. Calves produced is closely correlated with the age of an animal; therefore, older animals are more tetany prone. Fontenot (1979) suggested that older animals are perhaps more

susceptible to grass tetany because their labile Mg reserve found mostly in the bone is lowered. Similar conclusions were drawn by Kemp et al. (1961). Smith (1957, 1959a) indicated that calves have a decreasing ability to utilize Mg with increasing age which would further support age as a factor in this disorder. There is no doubt that animals more susceptible to hypomagnesemia are not receiving adequate Mg to maintain the body's requirement whether it be due to less Mg available in lush pastures, increased milk Mg secretion, or decreased absorption and retention.

Clinical Signs

The observable signs of grass tetany include undue excitement, incoordination, muscular twitching, profuse salivation, grinding of teeth, general tetanic contractions, labored breathing, pounding heartbeat, convulsions, and death (Blaxter et al., 1954; Rook and Storry, 1962; Grunes et al., 1970; Fontenot, 1979). Underwood was cited by Grunes et al. (1970) as characterizing a chronic form of hypomagnesemia by a stiff gait and gradual loss of condition, which can occur for several weeks without affecting appetite or milk yield followed by the clinical signs if low Mg is maintained.

Parr (1957) conducted an experiment in which hypomagnesemia was induced in milk fed calves. He was very descriptive in his observations:

> The earliest signs of abnormality were nervousness and a brighter appearance to the eyes. This was followed by

> increased hypersensitivity, flapping of the ears, chomping of the jaws, kicking at the abdomen and swishing of the tail, giving a general agitated appearance to the animal. Sometimes the animals experienced difficulty in drinking from buckets and would sway their heads as if to try to determine their exact position. Convulsions were not usually seen until a few days after the appearance of these symptoms. Scouring, with dark brown feces, sometimes preceded the onset of convulsions by one or two days. Convulsions were often precipitated when blood samples were being taken or during feeding. The convulsions were accompanied by marked exophthalmos, opisthotonus, and salivation.

It was suggested by Duncan et al. (1935) that young calves are more able to withstand numerous convulsions but older calves usually succumb to the first attack.

With death occurring during a tetany episode, post-mortem findings have shown extensive hemorrhages coupled with acute congestion of internal organs (Rook and Storry, 1962). The predominant post-mortem change in calves is the extensive hemorrhages principally in the pleural cavity. Hemorrhages are very marked on the epicardium and endocardium, throughout the cardiovascular system, the thymus, lungs, and muscles. The heart values tend to be reddened and sometimes edematous. Most calves have some thickened areas of the pericardium resembling a pericarditis-like-condition. The liver may be enlarged and the gall bladder is usually full of viscous bile. Kidneys may be enlarged and occasionally show gross degeneration (Moore et al., 1936; Thomas, 1959; Blaxter et al., 1954; Parr, 1957). Thomas (1959) stated that older calves have had areas of visible calcification on the endocardium with this calcification occurring more frequently in Jersey than Holstein calves.

Requirements

Rook and Storry (1962) suggested that the minimum dietary requirement of Mg for growing dairy heifers is 2.10 g daily at 150 lb. liveweight, and 6.40 g daily at 1200 lb. liveweight. Thomas (1959) established that calves require from .6 to 2.1 g Mg per 100 lb. bodyweight. It is obvious that a lactating animal would require more Mg than a growing one; therefore, according to Fontenot (1979) the calculated dietary Mg requirement would be 20.9, 22.1, and 18.0 g per day for cows at 35, 95, and 155 days of lactation, respectively. This is based on the assumption that 2 mg of Mg/100 ml of blood serum would be the minimum safe level. Fontenot (1979) further suggested that in order to meet these requirements forages would need to contain .18, .19, and .16% of available Mg dry basis for the respective stages of lactation.

Treatment

Hypomagnesemia may result from a simple Mg deficiency due to low levels of intake or from factors which lower the efficiency of utilization of this mineral element. It was found that feeding a high dietary K level (4.5%, dry basis) increased fecal Mg and decreased its absorption to the same extent, expressed as grams per day, with widely different Mg intakes. Thus, it is assumed that a depression in Mg absorption can be overcome by simply feeding additional Mg (Fontenot, 1979).

There are numerous available methods to attempt to increase the Mg intake of a particular animal, either by increasing available

Mg in the plant or increasing the available Mg to the animal itself by supplementation. Fertilization and foliar applications of Mg have had limited success; however, weather plays an important role. Rain quickly washes Mg slurries from treated forages (Grunes et al., 1970; Reynolds, 1980). Grunes et al. (1970) cited Ritchie and Hemingway in demonstrating that Mg alloy rumen bullets would slowly release Mg and have been effective in decreasing the incidence of hypomagnesemic tetany in dairy cattle; however, there was not a pronounced effect on increasing Mg in the blood. Studemann (personal communication) demonstrated a lack of success using Mg alloy rumen bullets. A bullet containing 280 g of Mg released approximately 1 g per day.

Oral supplementation seems to be the most widely used method in maintaining plasma Mg concentrations. Rook and Storry (1962) calculated that cattle need 50 g of MgO per day given as a drench or mixed with supplemental feed and Grunes et al. (1970) approximated that calves require 3.7 to 7.0 g of Mg (7-15 of commercial grade MgO per day) depending on their age. These levels are in agreement with other research conducted.

Certain geographical areas may be more prone to the occurrance of tetanic convulsions associated with hypomagnesemia; therefore, rapid effective measures to increase plasma Mg are essential. The most widely used treatment for a tetany episode is intravenous administration of Ca + Mg gluconate with added boric acid, dextrose, and phosphate. Research has shown that

after administration of this solution if the animal is not removed from the tetany producing pasture the plasma level of Mg can become dangerously low by 24 to 37 hours post injection (Grunes et al., 1970). Meyer and Busse (1975a) demonstrated that an intravenous injection of Mg gluconate would increase the CSF a level of .4 mg/100 ml in Mg deficient sheep. Data has been documented that the CSF depletion may initiate tetanic convulsions; therefore, this increase in Mg concentration could be crucial. Littledike and Cox (1979) established that a 20% solution of $MgSO_4$ (200-300 ml) injected intravenously maintains increased serum Mg concentrations for three to six hours. A similar solution injected subcutaneously increased serum Mg slightly less but the increase was more prolonged. Ritchie and Hemingway (1963) concluded that 6.6 g of MgO given as a drench to ewes did not increase plasma Mg values as measured at 24 hours post dosing; however, plasma increased by .5 mg of Mg/100 ml 4 hours after drenching. Wilson (1980) supplemented hypomagnesemic cows orally or by subcutaneous injection with 2 g Mg per day as $MgSO_4 \cdot 7H_2O$. Supplementary Mg significantly increased plasma Mg concentrations regardless of the route of administration.

A rectal infusion of 30% $MgCl_2 \cdot 6H_2O$ solution has proven to be a very effective method in increasing the plasma as well as CSF Mg in cattle. This has been shown by Meyer and Busse (1975b) and Bell et al. (1977). Bell et al. (1977) indicated that using 60 g of $MgCl_2 \cdot 6H_2O$ into 200 ml of water as a rectal infusion

would increase the plasma Mg level significantly within 20 minutes which is obviously effective during a critical tetany episode.

Calves as Models

Numerous researchers have studied the effects of hypomagnesemia in milk-fed calves (Blaxter et al., 1954; Smith, 1957; Parr, 1957; Smith, 1959a,b). Calves are effective models because the financial burden of possibly losing an adult cow as an experimental unit is not apparent. Most tissue and induced tetany data has utilized calves; however, most Mg absorption data has utilized canulated sheep. Reynolds (1981) used calves to collect data on rectal infusions of 30% $MgCl_2 \cdot 6H_2O$ solution as an emergency procedure during tetany episodes. This data demonstrates the effectiveness of calves as models for this type of experiment.

II. MAGNESIUM HOMEOSTASIS

Physiological Function

Mg is primarily an intracellular ion and is an important cofactor in the activity of many enzyme systems, particularly those involving adenosine triphosphate (ATP). These systems are concerned in the utilization of energy for synthesis and transport in and out of cells (Wilson, 1964). It is well documented by many researchers that ATP is required by most of the energy requiring biological systems including membrane transport, amino acid activation, acetate activation, succinate activation, protein

synthesis, nucleic acid synthesis, fat synthesis, coenzyme synthesis, nerve impulse generation and transmission, muscle contraction, and oxidative phosphorylation. Therefore, Mg must play some role in all these processes (Grunes et al., 1970). Wilson (1964) concluded that the Mg present in the extracellular fluid is important in nerve conduction, transmission of myoneural functions and muscular contraction. Mershon was cited by Grunes et al. (1970) in which he suggested that Na and K propagate the electrical potential at the membrane surface, and Ca and Mg stabilizes the membrane. Further, the normal impulse transmission depends on the antagonistic effects of Ca and Mg ions on the synthesis and release of acetylcholine (ACH). When Ca ions are relatively less depleted than Mg ions in tetany, the rate of spontaneous ACH release increases. Tetany results, then, from the increased irritability and spontaneous discharge of the sensory, motor, and muscle fibers.

Research has been conducted that supports the evidence of Mg involvement in ATPases and specific enzyme systems. When rats were fed a Mg-deficient diet there was a significant decrease in intestinal Mg-ATPase relative to the controls despite having no significant decrease in intestinal Mg levels (Watkins and Martin, 1982). Hsu et al. (1982) substantiated that the concentrations of erythrocyte glutathione (GSH) were reduced in male and female rats receiving a Mg-deficient diet and had a reduced blood ATP level. These findings suggest that Mg is essential in the

maintenance of GSH concentration to protect against oxidative damage in the erythrocyte membrane.

Absorption

Mg absorption by the gastrointestinal tract as well as the availability of Mg have been of major concern in better understanding the etiology of hypomagnesemia. Factors which influence the availability, range from binding of Ca and Mg to the digesta to mineral interrelationships. There are very few estimates of the true availability of Mg in feedstuffs; this is because of the difficulty in estimating endogenous excretion (Aikawa, 1981). Rook and Storry (1962) estimated that the net absorption of Mg is usually around 20% of the intake, ranging from 5 to 40% and in general seemed to be independent of intake which is similar to the 17% Kemp et al. (1961) determined in pasture sources. The apparent absorption of Mg of three month old calves was 35% as indicated by Perry et al. (1967) which is similar to results reported by Smith (1959b) who further demonstrated that this absorption appeared to be independent of intake. These higher values than reported by Rook and Storry (1962) are probably due to some age factor. Smith (1959a) reported Mg absorption in calves decreases with age.

The earliest studies of Mg absorption suggested that Mg was absorbed from the middle third of the small intestine. Other areas of the digestive tract of the ruminant were not considered important

under normal dietary conditions. Stewart and Moodie (1956) dosed sheep with Mg salts and collected venous blood from different sites of the alimentary tract. They demonstrated that after dosing with 122 g of $MgSO_4$, the principle site of Mg absorption is probably the duodenum and small intestine. Phillipson and Storry (1965) found similar results when it was demonstrated that the rumen epithelium appeared to be relatively impermeable to both Ca and Mg. Research by Care and Van't Klooster (1965) indicated that Mg was absorbed from the upper ileum in sheep and appeared to reach a limiting value with increasing intraluminal Mg concentration. It was postulated that the rumen does not appear to be an important site of net absorption when Mg concentration is within normal limits; however, after supplementation with 37.6 g of Mg acetate absorption increased. Similar findings were reached by Smith (1957, 1959a,b) using calves as experimental models.

More recent works have demonstrated that the rumen is the major site of absorption with some absorption occurring in the large intestine with the small intestine more involved in net secretion of Mg back into the tract (Grace, 1970; Pfeffer, et al., 1970; Grace et al., 1974; Stevenson and Unsworth, 1978). When a low Mg diet was fed to four canulated sheep, Tomas and Potter (1976a) found that the Mg infused into the abomasum or omasum was completely recovered at the duodenum, indicating a lack of net absorption of Mg from these stomach compartments. In contrast,

13.7 to 18.7 mmol (36-61%) of the Mg infused into the rumen was not recovered at the duodenum suggesting a substantial net absorption. The post-ruminal infusion of Mg was associated with decreased plasma and rumen Mg concentrations, decreased urinary Mg excretion, decreased Mg balance, and increased fecal Mg excretion which was in direct conflict with Field and Munro (1977) data. This data by Tomas and Potter (1976a) supports the concept of ruminal absorption because absorption of Mg post-ruminally is apparently insufficient to maintain normal Mg status of the animal. Total absorption from the entire gastrointestinal tract was 44.4% of intake for the intra-ruminal infusion and 3.75% for the post-ruminal infusion; therefore, the reticulorumen accounted for 70 to 91% of the total Mg absorption. Similar results were demonstrated in another experiment by Tomas and Potter (1976b) in which $MgCl_2$ was infused into different sections of the tract. However, Horn and Smith (1976) have indicated that absorption occurred in the omasum rather than the reticulorumen.

Data seems to remain uncertain about the concentration or even the possibility of a net secretion of Mg into the small intestine. Axford et al. (1975) using sheep as models, on adequate Mg rations demonstrated that there was no net absorption or net gain of Mg by digesta passing through the small intestine. However, in direct contradiction, Ben-Ghedalia et al. (1975) indicated that in the last 10 m of the small intestine of sheep considerable amounts of minerals were secreted; .70 and .96 mmol of Ca and Mg,

respectively. Perry et al. (1967) demonstrated similar results in three month old calves using an unabsorbed marker.

Absorption of Mg from the large intestine was demonstrated by Smith (1957, 1959a) with milk-fed calves. Smith concluded that about 40 to 70% of the Mg escaping absorption in the small intestine was absorbed in the large intestine. Smith also demonstrated that in young calves (age two to five weeks) the mean net absorptions up to the distal end of the small intestine and in the large intestine respectively were about 25 and 35% of intake and absorption through the large intestine decreased with age. Numerous other data has been compiled that support the theory of the large intestine contributing to absorption (Pfeffer et al., 1970; Ben-Ghadalia et al., 1975; Thomas and Potter, 1976b; Stevenson and Unsworth, 1978). Researchers have demonstrated dietary Mg absorption throughout the gastrointestinal tract; however, the reticulorumen probably contributes more than any other section of the tract.

The mechanism by which Mg absorption takes place is most likely a process that involves some active transport; however, some of the earlier data (Rook and Storry, 1962) collected indicated passive diffusion from the intestines into the blood. Brown et al. (1978) established pouches in the dorsal rumen sac of sheep to investigate the nature of the absorptive process. The results demonstrated that the potential difference between the pouch solution and venous blood was 25 $\pm$ .71 mv which support

the theory that Mg is transported actively against an electrochemical gradient. Field and Munro (1977) using different Mg infusion rates (.44-2.9 g/day) in sheep indicated similar results. The mechanism by which the transfer of Mg across isolated rumen epithelium occurs was studied by Martens and Harmeyer (1978) using a ^{28}Mg tracer technique. Their data substantiated that isolated epithelium of the rumen is permeable to Mg ions which is in contrast with work by Phillipson and Storry (1965). They determined several characteristic features common to other active processes. The data suggested net transepithelial efflux in the diretion from lumen to blood in the absence of a concentration gradient; therefore, the net transfer of Mg is an uphill movement. Secondly, the transfer appears to be at least partly dependent upon a functional Na^+-K^+ transport system in the mucosa. Inhibition of the Na^+-K^+ ATPase by ouabain, a chemical inhibitor of the mechanism, reduced net movement of Mg by 90%. It was also demonstrated that the passage of Mg across the epithelium from lumen to blood is saturable and temperature sensitive. Finally, the amount of Mg which is transported depends largely on the duration of the in vitro experiment which supports the view that the transport depends on the supply of metabolic energy and on a viable, intact epithelium structure.

With respect to absorption of Mg from the intestinal area, Care and Van't Klooster (1965) conducted studies with infusion of Mg into different portions of the digestive tract of sheep. It

was suggested that Mg may be absorbed from much of the ileum of sheep by a process of facilitated diffusion involving a limited carrier system which is common to Ca ions. In fact, it was suggested as a possible explanation of high Ca concentration interference with Mg absorption. Behar (1974) designed an experiment to characterize the mechanism of Mg transport with respect to its interaction with sodium, sugars, and bulk water flow in the rat ileum and colon. His theory is that Mg is transported by a solvent drag mechanism. The results indicated that the magnitude and direction of water movement had a marked effect on Mg transport and that sodium, urea, hypotonic solutions, and sugars may stimulate Mg transport by generating bulk water flow. An additional mechanism of active transport, perhaps passive ionic diffusion is also suggested because tissue accumulations of Mg levels are above those of the luminal concentration. Behar (1975) found results that are consistent with the solvent drag theory; however, an increase in tissue accumulation was associated with a decrease in net sodium absorption again suggesting an additional mechanism of Mg transport operating independently of the net water flow. Tomas and Potter (1976a) presented conflicting data suggesting that the net transepithelial flux of water from the rumen is sufficient for only a small proportion of the estimated Mg absorption since rumen fluid Mg levels averaged only 2.54 mmol per litre during ruminal influsion. Also, the

results suggest that the mucosa of the ruminant forestomach may not be freely permeable to the bulk transfer of Mg.

There may be more than one mechanism by which Mg is transported across the epithelial tissue depending on numerous factors such as diet, Mg concentration, and other minerals present. However, one could conclude that some amount of active transport occurs due to the electrochemical gradient present in the tissue.

Excretion

It has been established that the main excretory pathway of Mg is via the feces, which contain unabsorbed and endogenous sources of Mg. The endogenous fecal Mg is derived from unabsorbed digestive secretions and from desquamated epithelial cells of the tract. Saliva and gastric juices are also two important endogenous sources of Mg. Rook and Storry (1962) determined that the Mg content of mixed, parotid, submaxillary or residual saliva in sheep ranges from .5 to 1.4 mEq per liter with values for gastirc juice, bile, pancreatic juice and the secretions of Brunner's glands and cecum to contain .7 to 2.5 mEq per liter. This represents a total of 16 mEq per liter, an amount similar to that of the extracellular fluid. Simesen et al. (1962) calculated the mean endogenous excretion in calves to be about 3.5 mg/kg on a simple bodyweight basis and that of mature cows to be 1.5 mg/kg bodyweight. Direct estimations of fecal Mg on diets low in Mg have given comparable values of 2.2 to 4.0 mg/kg bodyweight (Blaxter

Rook, 1954) with calves from two to five weeks of age excreting 0.5 mg/kg bodyweight in endogenous Mg (Smith, 1957). To study the correlation between fecal and urinary losses of Mg, Lomba et al. (1968) fed 41 different rations to 127 adult non-pregnant dry cows. It was demonstrated that the fecal endogenous losses of Mg can be highly variable. Simeson et al. (1962) indicated that endogenous excretions vary with the amount and type of diet which is similar to that concluded by Field (1962). Rook and Storry (1962) concluded that since the contribution of Mg in saliva is relatively important, diets containing a high proportion of roughage or pasture may be associated with high endogenous fecal losses of Mg, thereby reducing the availability. Endogenous excretion of Mg has been shown to remain constant in control and hypomagnesemic animals (Rook and Storry, 1962); however, total fecal Mg is reduced (Storry and Rook, 1963). Van't Klooster (1969) has suggested that the ultrafilterable Mg was much lower when grass or a tetany inducing ration was fed to cattle. McAleese et al. (1961) demonstrated that even though the percentage of ^{28}Mg excreted in the feces from an intravenous injection was small, control lambs excreted a larger amount than deficient lambs. When an oral dose of ^{28}Mg was administered, control lambs excreted twice as much Mg in the feces as deficient lambs.

Typical results have demonstrated that the amount of Mg excreted in the urine is always small relative to that in the feces. The urinary excretion of Mg accounts for approximately 5%

of the total excretion (Blaxter and Rook, 1954). Field et al. (1958) concluded that a change in Mg intake was directly related to urinary Mg levels in wethers. Rook and Storry (1962) suggested that the urinary excretion of Mg reflects the nutritional adequacy of a diet, and the transfer of an animal to a diet deficient in Mg is followed by a fall in serum Mg and urinary excretion until at a threshold level excretion of Mg ceases. Similar conclusions were drawn by Kemp et al. (1961) in which urinary excretion of 1 g or less was highly correlated with hypomagnesemia. In fact, Kemp et al. (1961) suggested that the daily excretion of Mg in the urine appeared to be a better measure of Mg status in an animal than plasma values.

Some researchers (Kemp et al., 1961; Rook and Storry, 1962; Storry and Rook, 1963) have concluded that a close correlation exists between plasma and urine Mg levels; however, Field (1962) stated that no correlation between serum Mg concentration and the amount in the urine was detected. Rook and Storry (1962) suggested that urinary excretion appears to be controlled by a filtration-reabsorption mechanism in which Mg acts as a threshold substance, appearing in the urine only when the Mg load filtered by the glomeruli exceeds that reabsorbed by the tubules with the threshold level being approximately 1.8 mg/dl in cattle which is close to plasma Mg levels. This is in complete agreement with Meyer (1976a).

Magnesium in Body Fluids

Approximately 40% of the body Mg is distributed equally between muscle and nonmuscular soft tissues (Aikawa, 1981). Approximately 1% of the total body content of Mg is extracellular according to Wilson (1964). He concluded that the regulation of the amount of Mg in the extracellular fluid (ECF) is of the most importance since this in turn involves consideration of the concentration in othe tissues and retention of the element.

According to Aikawa (1963) and Wilson (1964) Mg is very much like K in that it is predominately located within the cells. Aikawa (1963) continues on to conclude that although serum Mg represents only a small amount of the body content of Mg, it is this proportion that is most accessible for chemical analysis, and hence clinically important. Data has shown that healthy animals will have a plasma or serum Mg concentration between 1.7 and 3.0 mg per 100 ml, and that symptoms of nervous origin are likely to occur at lower than 1.2 mg per 100 ml (Rook and Storry, 1962; Wilson, 1964).

Approximately one third of the extracellular Mg is bound nonspecifically to plasma proteins, the remaining 65% which is diffusible or ionized, appears to be biologically active (Aikawa, 1981). Wilson (1964) concluded similar findings and indicated that *in vitro* experiments have shown that the Mg ions and Mg proteinate are interrelated by a simple dissociation equilibrium which is:

$$MgProt \rightleftharpoons Mg^{+2} + Prot^{-2}$$

and governed by the law of mass action. In vitro the equilibrium is influenced by pH, the lower the pH the higher the concentration of ionic Mg. This theory may have some correlation with the amount of Mg absorbed from the gastrointestinal tract.

Care (1967) suggested that the body contains a central Mg pool which can be considered an index of the overall metabolism of Mg. It amounted to 1.7 mEq of Mg per kg lean body mass per day. However, the data indicated that when hypomagnesemia was produced there was a reduction in the turnover rate of Mg in the central pool to 1.1 mEq of Mg per kg lean body mass per day and this reduction was not accompanied by a redistribution between the central and outer pools.

Plasma clearance studies with ^{28}Mg established that the element is removed fairly rapidly and distributed to tissue or excreted. McAleese et al. (1961) dosed Mg deficient and control lambs both orally and intravenously with ^{28}Mg. Results showed that plasma disappearance of the intravenously administered dose was very rapid during the first two hours followed by a slower disappearance until approximately 8 to 10 hours later when most activity was gone. With the oral dose, plasma ^{28}Mg reached a maximum at 12 to 14 hours post dosing. Whatever the control over Mg homeostatis, the concentration of ionized Mg in the plasma probably plays a key role.

Cerebrospinal fluid is essential for the proper functioning of the central nervous system. It is located in the ventricles

of the brain, where it is formed by the choroid plexuses, and in the subarachnoid space surrounding the brain and spinal cord. The CSF is a combination of transudate which passively crosses the capillary vessel wall and an active secretion by the ependymal cells (Frandson, 1976).

Meyer and Scholz (1972) calculated that the Mg level of CSF in sheep (n = 26) was 2.37 $\pm$ .14 mg/100 ml with an influence of age, sex, or sedation not observed. In cattle (n = 28) the average Mg content of CSF was 2.26 $\pm$ .16 mg/100 ml which is in agreement with that concluded by Aikawa (1981). Due to the higher concentration of CSF Mg to plasma Mg the blood-brain barrier must be intact (Aikawa, 1963). According to Littledike and Cox (1979) the CSF is believed to be in ionic equilibrium with the interstitial fluid of the CNS.

There does not appear to be a simple relationship between the diffusable Mg of the serum and CSF Mg. The Mg exchange between plasma and CSF was studied in dogs using $^{28}MgCl_2$ and $MgCl_2$ by Oppelt et al. (1963) Results demonstrated that the normal CSF/plasma ratio in dogs is 1.34 and while plasma Mg increased 300 to 400% post dosing, the CSF Mg only rose to a maximum of 21% above the control over a 5.5 hour period. The exit rate of Mg from the CSF has a half-time of approximately 70 minutes and was not affected by increasing plasma concentrations. These data suggest that an active transport mechanism is involved in movement of Mg from the blood to the CSF and that diffusion and bulk filtration are responsible for movement out of the CSF.

In recent years a positive correlation has been found between severe hypomagnesemia and lower CSF Mg levels (Meyer and Scholz, 1972; Pauli and Allsop, 1974; Meyer, 1976b). Pallis et al. (1965) found similar indications that lowered CSF in human patients was associated with neurological disorders. Meyer and Scholz (1972) conducted an experiment in which sheep were fed a low Mg ration. In a progressive, Mg deficiency the Mg content in the CSF decreased to lower than 1.4 mg/100 ml; however, this decrease took 60 days to obtain in young animals and only four days in older, lactating ewes. It was concluded that the Mg content of the CSF was more related to clinical signs of tetany than plasma levels obtained. At Mg levels lower than 1.6 mg/100 ml in the CSF clinical signs were at risk; at 1.2 mg/100 ml tetany occurred on a regular basis (Meyer, 1977). These values were further supported with the perfusion of Mg-free CSF in sheep (Meyer et al., 1974).

A study was conducted with rats fed a Mg deficient diet in which Chutkow and Meyers (1968) found that the CSF Mg remained normal for the first 24 hours of Mg restriction; however, then decreased for 8 to 13 days thereafter. The analysis of brain Mg appeared to be 98% intracellular which decreased exponentially after day one in which hyperexcitability was closely correlated with the lower Mg content. In contrast, Meyer (1977) found no lowering of brain Mg in sheep dying of hypomagnesemic convlusions. These studies provide evidence that the mechanism

of clinical signs of Mg deficiency are derived from the CNS rather than peripherally. However, an experiment conducted by Todd and Horvath (1970) indicated that the CNS was not involved in tetanic convulsions. Reynolds (1981) showed that Mg enemas given to calves with low blood and CSF Mg increased these levels of Mg. However, when Mg enemas were given to calves with normal CSF levels there was only an increase in plasma Mg.

Allsop and Pauli (1975a,b) developed a useful technique of ventriculolumbar perfusion of the CSF space in sheep to better understand the mechanisms by which CSF is involved in hypomagnesemia. Results indicated that perfusion with synthetic CSF solutions containing less than .6 mg of Mg per 100 ml produced episodes of tetany which were abolished by perfusion with a solution of normal concentration of Mg.

Magnesium added to the CSF directly has been shown to have other effects on the CNS of an animal. Results of an experiment by Feldberg (1957) concluded that 2.0 to 5.0 mg of $MgCl_2$ injected directly into the cisterna magna caused an anaesthesia like condition in cats which is the opposite effect of low Mg levels. Mg infused into sheep elicited dose dependent feeding responses with Ca responding the same; however, K+ inhibited the feeding responses of both Ca and Mg (Seoane and Baile, 1973).

Better understanding the mechanisms by which hypomagnesemic tetany occurs through research on CSF can be very beneficial; however, animal variation remains a primary factor of this syndrome.

An experiment conducted by Sims et al. (1980) supported this continuous animal variation in response to tetany. Adult wethers were fed diets deficient in Mg which produced plasma Mg levels as low as .3 mg per 100 ml; however, CSF, Ca, K, and Mg was not altered throughout the experiment.

Magnesium in Tissues

Bone contains 60% of total body Mg and supplies a crucial reserve of labile Mg; however, Mg in the soft tissues remains constant (Blaxter and Rook, 1954; Fontenot, 1979). The Mg content of the soft tissues varies widely from .06 to .13% of the dry matter and is concentrated in the cell's nucleus, bound by such substances as ribonucleic acids (Rook and Storry, 1962). There are considerable differences in content among tissues; however, if due allowance if made for the presence of extracellular Mg in the cells, the concentration is approximately 30 meg per liter (Wilson, 1964; Aikawa, 1981).

According to Wilson (1964) experiments conducted with ^{28}Mg have indicated that the rate of exchange of Mg between plasma and tissue is rapid in liver, kidney, and heart. In the brain and skeletal muscle on the other hand, exchange takes place in two states; there is a rapidly exchanging component which has a turnover time of 1 to 1.5 hours and a slow component with a turnover time of 24 hours. Work conducted by McAleese et al. (1961) demonstrated that deficient lambs dosed with ^{28}Mg had the highest Mg concentrations in the heart and liver, 35 hours post-dosing.

The data further indicated that most soft tissues contained a higher concentration of ^{28}Mg than bone and teeth.

Most research conducted (Blaxter et al., 1954; Wilson, 1964; Littledike and Cox, 1979; Miller et al., 1981) has demonstrated similar conclusions that Mg concentration of soft tissues does not deplete, in hypomagnesemic animals, as compared to normal animals. McAleese et al. (1961) found that after dosing control and Mg deficient lambs with ^{28}Mg, the soft tissues from the deficient lambs were higher in ^{28}Mg concentration than control lambs. The concentration of ^{28}Mg was highest in the heart, then the liver, spleen, and kidney; however, in terms of total intake the liver contained the largest amount. A greater transport of Mg to tissues of deficient animals would be required to maintain tissue Mg equal to that of normal animals.

Tissue depletion of magnesium may not occur, but depletion of bone Mg in deficient animals is well documented (Blaxter et al., 1954; Parr, 1957). It was concluded by Wilson (1964) that in young rats and calves on Mg deficient diets there is a fall in the concentration of bone Mg by 30%. Similar results have been indicated from numerous data compiled. Smith (1957) concluded that the Mg content of bone decreases as the age of a calf increases and 60 to 80% of the Mg retained by a normal calf is laid down in bone which would be expected. Even though bone has a large reserve of Mg it is probably not a significant source of Mg in the classic cases of grass tetany occurring in cattle on lush spring pasture.

III. FACTORS AFFECTING UTILIZATION

Age of Animal

There are many factors which may significantly affect the utilization of Mg by decreasing absorption. Smith (1957, 1959a) has conducted numerous experiments with milk-fed calves. Results collected have indicated that as a calf gets older its ability to absorb Mg is decreased which is attributed to a decrease in the absorptive function of the large intestine. Garces and Evans (1971) fed 12 Jersey steers ranging in age from 10 to 88 months six different diets varying in nitrogen sources. Age of the animals and time during treatment did not have any significant influence on apparent absorption of Mg. Chicco et al. (1973b) established that plasma Mg decreased more quickly, and voluntary feed intake was reduced sooner in mature sheep than younger animals.

Amount/Type of Ration

The amount of Mg in the diet can affect the utilization of Mg and site of absorption. Perry et al. (1967) studied the intestinal distribution of Ca, Mg, Na, K, and N in calves fed different types of diets. Results indicated that no change occurred in the ruminal Mg concentration in relation to the feed ingested or in the Mg concentration in the intestinal content from the type of ration consumed.

Research has been compiled on the saturation rate of Mg in rumen tissue which is correlated to the amount of Mg ingested.

Field and Munro (1977) carried out balance trials in which different amounts of Mg were infused into the stomach compartments of sheep. They concluded that the proportion of infused Mg which was absorbed from the stomach area fell from .61 to..14 as the infusion rate increased from .44 to 2.80 g per day. Similar results were concluded by Brown et al. (1978) with ewes. It was indicated by the results that the absorptive mechanism of the rumen was saturable at a concentration above 4 mm. The amount of feed fed indicated that absorption in the rumen was increased by 44% if animals had a continuous supply to feed vs. being fed once daily (Grace and Macrae, 1972).

Dietary Constituents

There seems to be a negative correlation between the crude protein content of a forage or diet and the Mg availability. Kemp (1960) indicated that as dietary protein content fed to dairy cattle increased, the available Mg decreased. Toothill (1963) concluded that an increase in the dietary protein increased the percent absorption of Mg from 71.7 to 73.8 in rats. Even though the percent of Mg retained by animals in the higher protein group was significantly higher, the quantity of Mg retained per unit gain in weight was slightly less than those consuming the lower protein ration. However, Grace and Macrae (1972) found no changes in Mg by the feeding of protein as did Moore et al. (1972).

High dietary levels may reduce Mg absorption by increasing the ammonium content of the rumen which in turn increases the pH. To study this possible effect Toothill (1963) used rats as models and fed various ammonia compounds; however, none had a significant effect on the apparent absorption of Mg. Henry et al. (1977) studied the effects of exogenous histamine and ammonia on hypomagnesemic labms. The lambs were ruminally fistulated and infused with histamine, ammonia, or a combination of the two. Lambs receiving the ammonia ruminally had lower serum Mg levels than those on other treatments with two lambs exhibiting signs of tetany. Ruminal ammonia levels were higher in groups receiving that treatment; however, rumen pH remained unchanged. Many researchers have concluded that an increased pH will decrease the solubility of Mg and, therefore, absorbtion (Ben-Ghedalia et al., 1975; Meyer, 1976a). However, the results by Henry et al. (1977) seem to indicate pH remains unchanged by the amount of protein being fed.

Some early spring pastures have been noted to contain not only low amounts of Mg but also low quantities of readily fermentable carbohydrates. To better study this as a contributing factor in hypomagnesemia, Madsen et al. (1976) fed sheep forage with or without supplemental glucose. Results indicated that supplementing the diet with glucose during high periods of risk may maintain plasma Mg levels thereby reducing tetany. In a related article Miller et al. (1976) concluded that absorption of

Mg was increased by glucose supplementation of a hay diet but urinary excretion of Mg was also increased, therefore, retention remained unchanged. However, this increased plasma Mg associated with supplementation may be due to an alteration in intermediary carbohydrate metabolism.

Lactose is another energy source implicated in hypomagnesemia. Forbes (1961) concluded that the addition of .25% lactose at the expense of glucose was accompanied by decreased weight gain, increased absorption, urinary excretion, and balance of Ca with increased urinary excretion and decreased Mg balance. In another experiment by Rayssiguier and Poncet (1980) it was determined that the addition of 400 g lactose per day significantly increased apparent absorption of Mg with absorption before the duodenum increasing from 19 to 41%. Fermentation of lactose in the rumen induced decreases in pH and ammonia.

Mineral Interrelationships

The effects of other minerals on the absorption of Mg have a major contributing factor in the etiology of hypomagnesemia with potassium having the most extensive effects. Other major mineral interactions are Ca and P or the combination of both which according to Jacobson et al. (1972) is more effective in accentuating Mg deficiency. Dutton and Fontenot (1967) conducted mineral balances on wethers to study the effect of dietary organic P on the metabolism of Mg. It was concluded that there was a significant interaction between level of Mg and form of P in the

diet with inorganic P causing a greater decrease in plasma Mg than the organic form. Phytate had no effect on absorption of Mg which would be expected in ruminants because of the presence of phytase in the rumen. Similar results were found by Wise et al. (1963) in which high dietary levels of P decreased plasma Mg. Chicco et al. (1973a) fed dietary levels of Ca, P, and Mg varying with Ca content of .13 to .78%, P .12 to .36%, and Mg 500 to 7,750 ppm to wethers to study the interrelationships of these minerals. High dietary Ca decreased Mg in the bone and plasma partly due to increased fecal excretion of Mg. Feeding increased levels of Mg did not influence fecal excretion of Ca or bone concentrations; however, excess Mg reduced both urinary and plasma Ca. Results indicated that increased Ca decreased Mg utilization while Mg had the same effect on Ca. This effect could be explained by the indication that Ca and Mg may compete for the same absorptive mechanism involving a limited carrier system for both minerals (Care and Van't Klooster, 1965). In wethers apparent Mg absorption, expressed as percent of intake, was significantly lower when fed a high P or high Ca diet which is supportive to the results indicated above (Toothill, 1963; Pless et al., 1973). Behar (1975) studied the effect of Ca on Mg absorption in rats in which results indicated an increase in luminal concentration of Ca led to a progressive decrease in Mg absorption. A consistent correlation was seen between net Mg absorption and rates of net water absorption at all Ca concentrations. This suggests that Ca

decreases Mg absorption by a reduction in membrane permeability to solutes that induce water flow which is consistent with the theory of Mg transport by solvent drag. The increase in the luminal concentration of Ca resulted in an increase tissue accumulation of Mg and decreased Mg absorption in the small intestine.

Cows may become severely hypomagnesemic less than a week after an abrupt change to early spring pasture. Ramsey et al. (1982) indicated that this has been attributed to reduced Mg intake, lowered Mg availability due to high K content of forage, or a combination of these factors. In an experiment conducted with wether lambs fed a low Mg high K diet, Ramsey et al. (1982) found that the addition of excess K to a low Mg diet increased the rate of plasma Mg decline over that due to low Mg alone. Numerous other researchers have concluded similar results with the addition of a high K intake by the ruminant animal (Kunkel, 1953; Fontenot et al., 1960; Bohman et al., 1969; Yano et al., 1982). In direct contrast to these results, a study was conducted with six mature ewes that were fed a 5% K ration with K added as bicarbonate in which the addition did not significantly influence the levels of Ca, Mg, or K in the serum of sheep (Pearson et al., 1949; Odell et al., 1952). Blaxter et al. (1960) indicated similar results in which sufficient K was added to a calf liquid ration to increase the serum concentration of K, to induce changes in nerve accommodation, and cause death in three calves; however, no effects on

Mg metabolism were recorded. The concentration of Mg in the serum, muscle tissue, and bone was unaffected by excess K and the onset of tetany was not accelerated due to this addition to the diet.

House and Van Campen (1971) indicated a plausible explanation for K effects on plasma Mg. It was suggested that a decline in plasma Mg was attributed partially to decreased Mg absorption, but mainly to a direct depressing effect of K on the circulating Mg. The absorption and retention of K increases in response to increased intake of this cation and it has been postulated that cells take up and retain more Mg as the level of K in the cell increases. House and Bird (1975) postulated a similar theory about the effect of high K lowering urinary Mg. Lentz et al. (1976) indicated that increased K intakes will increase insulin and glucose in Mg deficient calves. This had a direct depressing effect on plasma Mg by Mg being transferred into tissues, thus lowering serum Mg. Therefore, high K could exert an effect by altering intermediary metabolism in some way.

Excessive amounts of K fertilizers have been a contributing factor to this increased K intake by animals on pasture. Blaxter et al. (1960) indicated two possible ways that this might affect the incidence of hypomagnesemia and tetany. It is known that an excess of K will reduce the Mg concentration within the plants and secondly, excess soil K increases the K content of the plant; therefore, increases animal intake of this mineral. Data by Kemp (1960) verified that a heavy potash dressing on pasture leads to

substantial increases in K and chloride, with a reduction in Mg and Ca. However, Hemingway et al. (1963) indicated that K fertilizer use did not influence the plasma Mg or Ca levels of ewes, thereby indicating no effect on the plants consumed. Butler (1963) demonstrated that pastures associated with grass tetany had a significantly lower average Mg and sodium (Na) content and a higher K content than those which were classified as normal. This suggests a K effect.

It is apparent that the mechanism by which K reduces Mg plasma levels is due to an interference with the absorption of Mg. Tomas and Potter (1976c) researched the effect of KCl infusion into the rumen or duodenum of sheep upon the absorption of Mg from the stomach and intestinal regions. Net Mg absorption was lowered only when K was infused into the rumen, and the reduction was entirely due to reduced absorption of Mg from that area. There was no consistent effect on absorption of magnesium from the intestines. Plasma Mg levels were lowered by both the intraruminal and to a lesser extent the duodenum infusions of K. Since Mg absorption has been shown to primarily be in the reticulorumen, this appears to be the principle area of K effects on Mg. The intraruminal infusion imposed by Tomas and Potter caused a considerable increased bioelectrical potential between the rumen content and blood; therefore, they justify this as an increased barrier to transepithelial transfer of Mg, thereby reducing absorption. Similar results were indicated by MacGregor and

Armstrong (1979); however, they postulated that a change in the K:Na ratio of the rumen fluid increased the amoung of Mg flowing into the intestines as a result of hindered absorption.

Most recently, Greene et al. (1983b) fed cannulated wethers two levels of dietary Mg (.1 and .2%) and three levels of K (.6, 2.4, and 4.8%, dry basis) to determine how K affects Mg absorption. The data further verified that Mg is absorbed prior to the small intestine and that feeding 2.4 and 4.8% K decreased Mg absorption by 24.4 and 61.8%. However, unlike Tomas and Potter (1976c) that indicated no consistent decrease in intestinal Mg absorption, these results suggest a linear decrease in absorption from this area as K in the diet increases.

The effect of excess K on Mg absorption has in turn had a pronounced effect on the excretion patterns of Mg. Excess K intake is accompanied by a reduction in urinary excretion of Mg that appears to result from this lowered absorption (Fontenot et al., 1973; Frye et al., 1975). According to Suttle and Field (1967) adding K to the diet of sheep decreased urinary output of Mg by 33%. House and Van Campen (1971) conducted experiments using ^{28}Mg kinetics in which an increase in the intake of KCl significantly depressed Mg absorption, reduced urinary Mg excretion and lowered endogenous fecal Mg, but elevated total fecal output. However, Powley et al. (1977) indicated that daily endogenous fecal Mg excretion was not found to change in sheep fed an increased K or Na content in pasture. Greene et al. (1981) indicated that when

wethers were fed levels of K ranging from .6 to 4.8%, decreased preintestinal absorption of Mg occurred which resulted in larger amounts of Mg flowing into the small and large intestines and excreted in the feces. Most recently, Greene et al. (1983a) verified these results of increased fecal excretion of Mg with decreased absorption due to high intakes of K.

Earlier work by House and Bird (1975) indicated that excess K increases the retention of Mg by the cell, thereby reducing urinary Mg excretion. However, more recently, DeGregorio et al. (1981) suggested that K as KCl tended to cause an increased filtered load and absorption of plasma Mg which may contribute to this effect of decreased urinary Mg.

Nitrogen has also been suggested as a culprit in lowering Mg absorption and thus resulting in hypomagnesemia. In earlier studies, Kemp (1960) fertilized pastures with high levels of potash and N, finding that with higher K levels the K content in the pasture increases with the addition of a heavy nitrate dressing. The inverse relationship was found to occur at K levels in plants of less than 2% dry matter. He indicated that heavy potash and N dressings, whether separately or combined, cause a fall in serum Mg levels. Stillings et al. (1964) suggested that feeding forage with high applications of N fertilizer generally resulted in increased fecal Mg and decreased urinary Mg. Fontenot et al. (1973) indicated conflicting results from a two year study of fertilization with high levels of N. Results indicated a

depression of serum Mg only after the first year; however, urinary Mg excretion was lower for both years, therefore indicating a lower absorption of Mg.

Most recently, aluminum (Al) has been postulated to chelate Mg thereby reducing its availability. Allen and Robinson (1980) supported this hypothesis by showing that rumen contents of dead tetany animals contain 2,373 ppm Al, while non-tetany animal's rumen contents averaged 405 ppm Al.

CHAPTER III

EXPERIMENTAL PROCEDURE

I. GENERAL DESIGN

Twenty-six Holstein male calves were utilized from fall 1981 through fall 1982 to better understand the etiology of hypomagnesemia. The objective of this experiment was to produce hypomagnesemia in calves and to study the effects of excess K on Mg metabolism. Methodology included effects of two levels of oral drench repletion in calves with 30% $MgCl_2 \cdot 6H_2O$ solution on plasma and CSF mineral levels. Tissue samples collected for mineral analysis comparisons included lung, heart, brain, spleen, liver, skeletal muscle, rib, and kidney.

II. PROCEDURES AND MANAGEMENT

Animals

Twenty-six Holstein bull calves ranging from 3 to 15 days of age were obtained from The University of Tennessee's dairy over a period of one year. The calves were placed into individual metal pens with Dri-Dek[1] mats instead of bedding. All calves were placed on a commercial milk replacer[2] and offered a semipurified

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[1]Kendall Plastic Inc., Kendallville, IN.

[2]Tennessee Farmer's Cooperative, Lavergne, Tennessee.

basal diet and water ad libitum. Composition of the basal diet is given in Table 1. Bottles used to feed the milk replacer were cleaned after each use with Novasan Solution (Chlorhexidine)[3]. When the calves were consuming the basal diet in sufficient amounts, the milk replacer was gradually reduced. At approximately six weeks of age all calves were weaned. A difficulty that was encountered with weaning was the age differences and differences in weight thereby reducing uniformity. A major concern with the basal diet was bloat; therefore, to reduce the risk each calf was administered a few ml of proloxalene[4] on the back of the tongue at morning and evening feedings. However, this method was not entirely successful; therefore, the basal diet was modified to contain coarse ground corn cobs and more starch with a reduction in soy protein and dextrose. The composition of the modified basal diet is given in Table 2. When scours occurred, calves were treated with Sulkamycin-S Bolettes[5] for three consecutive days. If this treatment was not adequate in controlling the diarrhea, Biosol-M[6] and Kaopectate[7] was given orally.

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[3]Fort Dodge Laboratories, Inc., Fort Dodge, Iowa.

[4]Norden Laboratories, Inc., Lincoln, Nebraska.

[5]Norden Laboratories, Inc., Lincoln, Nebraska.

[6]The Upjohn Company, Kalamazoo, Michigan.

[7]The Upjohn Company, Kalamazoo, Michigan.

TABLE 1. Composition of Original Basal Diet

Ingredient	International feed number (IFN)	Composition (%)
Soy protein		22.1
Fine corn cobs[1]	1-02-783	10.0
Dextrose	4-02-125	42.3
Starch		20.3
Vegetable oil[2]	4-07-882	1.0
Mineral mix[a]		4.2
Vitamin mix[b]		0.1
[a]Mineral mix	IFN	Grams per 100 kg of feed
$CaCO_3$	6-01-069	1097
$CaH_4[PO4]_2 \cdot H_2O$	6-01-080	498
K_2HPO_4		498
NaCl	6-04-152	499
$FeSO_4 \cdot H_2O$		127
$CuSO_4 \cdot 5H_2O$		2
$CoSO_4 \cdot 7H_2O$		.096
ZnCl		9.6
$MnSO_4 \cdot H_2O$		16.6
$KHCO_3$		1476
MgO[3]		322
KCl[4]	6-03-755	6301
[b]Vitamin diet fortification mixture[5]		Grams per 100 kg of feed
Vitamin A (200,000 units per gram)		.45
Vitamin D (400,000 units per gram)		.025
Alpha tocopherol		.50
Ascorbic acid		4.5
Inositol		.50
Choline chloride		7.5
Menadione		.225
p-Aminobenzoic acid		.50
Niacin		.45
Riboflavin		.10
Pyridoxine hydrochloride		.10
Thiamine hydrochloride		.10
Calcium pantothenate		.30
Biotin		.002
Folic acid		.009
Vitamin B_{12}		.000125

TABLE 1 (continued)

[1]Grit o'cobs #4, The Andersons, Maumee, Ohio.

[2]CPC International, Inc., Englewood Cliffs, N.J.

[3]Substituted for some cerelose and starch in diets two and four.

[4]Substituted for some cerelose and starch in diets three and four.

[5]ICN Nutritional Biochemicals, Cleveland, Ohio.

TABLE 2. Composition of Modified Basal Diet

Ingredient	IFN	Composition %
Soy protein		20.0
Fine corn cobs	1-02-783	10.0
Coarse corn cobs[1]		10.0
Dextrose	4-02-125	18.0
Starch		36.7
Vegetable oil	4-07-882	1.0
Mineral mix[2]		4.2
Vitamin mix[2]		0.1

[1]M.S.P. Feed Company, Eatonton, Georgia.

[2]Same as original basal diet.

Treatments

Three separate trails were conducted through the fall of 1981 through the fall of 1982. Calves were randomly assigned to one of four diets, diet one was Mg deficient, diet two was adequate in Mg, diet three was Mg deficient plus 4% potassium, and diet four was adequate in Mg plus 4% potassium (Table 3). Diet four was eliminated in trial one because of the loss of two calves during the preliminary period. The composition of the modified basal diet is found in Table 2 and the mineral analysis of each modified diet for trial one, two, and three is found in Table 4. During trial two similar dietary constituents for all rations were mixed at one time and each ration was removed as MgO and KCl were added; therefore, diet four was last to be made. There is a difference of .54 mg/g of Mg between diet two and four due to the inconsistency in mixing rations in this manner. After the calves on the Mg deficient diets were below 1.0 mg of Mg/dl of plasma, the calves were placed into wodden metabolism crates (Briggs and Gallup, 1949) in which alterations were made to accommodate calves. While in the metabolism crates the calves were fed twice a day and offered distilled water three times a day which contained a minute quantity of Mg (<.05 mg/dl).

Calf Losses

Numerous calf losses occurred throughout the entire experimental period. At approximately the time of weaning in trial one, calf number four was found dead in the afternoon with bloat the

TABLE 3. Experimental Design

	Calves/Treatment			
	1 Mg Def.	2 +Mg	3 +K	4 +Mg+K
Trial 1	2	2	2	2
Trial 2	2	2	2	2
Trial 3	2	2	2	2

TABLE 4. Mineral Analysis of Diets (mg/g)

Mineral	Treatment Groups 1	2	3	4
	---------- Trial 1 ----------			
Magnesium	.20	1.89	.20	--
Calcium	5.91	6.54	5.99	--
Potassium	10.40	9.56	42.07	--
	---------- Trial 2 ----------			
Magnesium	.22	2.00	.19	1.46
Calcium	5.70	5.89	6.18	5.27
Potassium	9.86	9.17	41.92	42.44
	---------- Trial 3 ----------			
Magnesium	.16	2.15	.15	2.00
Calcium	6.18	6.01	5.86	5.34
Potassium	8.88	9.02	42.26	41.18

apparent cause of death. Later in the preliminary period of this trial, calf number eight went off feed and contracted pneumonia. The calf was fed a commercial electrolyte mix with glucose[8] throughout the day and night, however all measures failed; therefore, the calf was euthanized. An autopsy was performed which indicated the calf died due to starvation and complications from the virus. During the repletion phase of trial one, calf number seven never recovered from the anesthesia and died. Therefore, no repletion data was collected. Ten calves were obtained from the dairy for trial two to replace the calf losses from trial 1, however, three calves died during the period of trial two. Calf 14 died due to cardiac arrest during the preliminary period according to the necropsy report. This calf was fed diet four and the cardiac arrest was attributed to a high K plasma level (>28 mg/dl) and K imbalance. Another calf, calf number 10 succumbed to bloat after a balance was run; therefore, no repletion data was obtained. Calf number 11 was found dead which was attributed to heart failure during a tetanic episode. Eight calves were obtained for trial three however only six calves were used for the balance study because of the poor health of two of the calves. During the preliminary period calf number 119 developed severe bloat and was trochared to prevent death; however, the calf developed peritonitis and no data was collected. Also calf number 1909 had severe

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[8]Diamond Laboratones, Inc., DesMoines, Iowa.

chronic diarrhea throughout the balance period which prevented obtaining balance data; however, repletion and tissue data was collected. Also, calf number 33 died due to anesthesia during the repletion phase and no repletion data was collected from the animal (Table 5).

III. DATA COLLECTED

Balance Phase

After the calves were placed into metabolism crates a five day adjustment period and five day balance trial was conducted. During the collection period the daily feed consumption, urine, and fecal outputs were measured and recorded for each individual calf. Daily samples of refused feed and daily aliquots (2%) of the feed consumed by each calf were obtained for mineral analysis of the respective diets fed. Total daily urine output was measured and aliquots (2%) were collected and stored in glass jars. Fecal samples were collected twice daily by the use of canvas collection bags with a harness apparatus. The canvas bags were lined with a plastic bag at morning and evening feedings to collect the fecal matter with aliquots of feces (20%) being collected and composited daily. All feed, fecal, and urine samples obtained were stored under refrigeration.

Repletion Phase

Immediately following the balance phase of the experiment each calf was used to collect repletion data. The procedures used

TABLE 5. Calf Losses Due to Dietary Treatment

	Treatments			
	Mg def.	+Mg	+K	+Mg+K
Death losses	2*	1	1	1
Tetany	3	0	2	0

*Number of calves.

took considerable time therefore no more than two or three calves could be repleted per day. During trial one the procedure of CSF catheter placement was done in the metabolism room; however, trial two and three repletion procedures were conducted under more aseptic conditions in The University of Tennessee's Veterinary Hospital. Each calf was anesthetized using Bio-tal (sodium thiamylal)[9] and placed on a surgical table in right lateral recumbency. The calves' head was manually flexed ventrally and immobilized. A spinal needle with a stylette was then inserted through the skin, subcutaneous structures, and nuchal ligaments. Then the needle passed through the atlanto-occipital junction until the dura mater and arachnoid were penetrated and the needle was located in the cisterna magna. Then approximately 6 cm of flexible plastic tubing was threaded into the cisterna magna. A baseline CSF sample of 2 to 3 ml was obtained and a plug was placed on the tubing. This collection apparatus was then sutured directly behind the poll of the calf. After placement of the CSF catheter an I-CATH intravenous catheter[10] was placed into the jugular vein and taped to the neck. These catheters facilitated CSF and blood sampling.

During each sampling period approximately 1 to 2 ml of CSF was obtained with a syringe and 12 ml of blood was taken from the jugular catheter into heparinized syringes. Each CSF sample was transferred to a 5 ml plastic tube and blood samples

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[9]Bio-Ceutic Laboratories, Inc., St. Joseph, Missouri.

[10]Demed, Inc., Canton, Massachusetts.

were transferred to 50 ml heparinized centrifuge tubes. After baseline CSF and blood samples were obtained an oral drench of 30% $MgCl_2 \cdot 6H_2O$ solution was administered. The drenching apparatus consisted of a 200 ml wash bottle adapted to use a pliable plastic fluid feeder[11] attached. Subsequent blood and CSF samples were obtained at 5, 15, 30, 60, 120, and 180 minutes following the oral drench. The blood samples obtained were then centrifuged at 30,000 RPM for 15 minutes and the plasma was removed using disposable pipettes[12]. The plasma and CSF were then stored under refrigeration in plastic tubes until mineral analyses were determined.

Tissue Collection Phase

Within a 48 hour period after the repletion phase was completed each individual calf was euthanized with 12 ml of T-61 Euthanasia solution (N[-2-(m-methoxy-phenyl-2-ethyl-butyl-(1)]-gamma hydroxy butyr-amide)[13] via jugular puncture. Immediately after the calf was pronounced dead, it was opened from the sternum to the lower abdomen and tissue samples were obtained. Tissue samples were collected from the brain, heart, lung, liver, spleen, kidney, skeletal muscle attached to the femur, and the thirteenth rib. The samples were then placed into plastic bags and stored frozen until processed for chemical analysis.

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[11]The Magrath Company, McCook, Nebraska.

[12]Fisher Scientific Company, Pittsburg, Pennsylvania.

[13]American Hoechst Corp., Sommerville, New Jersey.

IV. CHEMICAL ANALYSES

Feed, Feces, and Tissues

Fecal samples were weighed, and placed into a 60°C drying oven for approximately five days. The samples were then removed from the oven and were air equilibrated for 24 hours, weighed, and dry matter determinations were calculated. A Wiley Mill with a 2 mm screen was used to grind the samples. Triplicate samples of approximately 1 g each were placed into crucibles, dried at 100°C for 24 hours, cooled, weighed, then ashed at 600°C for at least three hours. These samples were dissolved in 3 ml of 6N HCl, quantitatively transferred to glass test tubes and diluted to a known volume. To prevent phosphate interference, lanthanum trioxide (.1%) was added to all Ca and Mg dilutions and cesium chloride (.1%) was added to all K dilutions. A similar procedure was followed for feed and tissue analyses except those samples were not dried in a 60°C oven or ground in a Wiley Mill. All samples were analyzed for Mg, Ca, and K using an Instrumentation Laboratory Model 551 atomic absorption/ atomic emission spectrophotometer.

Urine

Triplicate 5 ml samples of urine were pipetted into crucibles containing ashless filter paper.[14] These samples were dried

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[14]Whatman Limited, England.

overnight in a 100°C oven, then ashed slowly, increasing the temperature until 600°C. At 600°C samples were ashed for approximately three hours. Samples were then put into solution by adding 3 ml of 6N HCl, quantitatively transferred to test tubes and diluted to a known volume for the same chemical analyses listed above.

Plasma and Cerebrospinal Fluid

These samples were diluted to a known volume and were analyzed in a similar manner as all other samples collected.

V. STATISTICAL ANALYSIS

Data was analyzed statistically using SAS programs prepared by Barr et al. (1979). Balance data was pooled within treatments because of the number of experimental units and analyzed by analysis of variance using the model:

$$Y_{ij} = u + d_i + e_{ij},$$

where:

Y_{ij} = dependent variables,

u = theoretical population means,

d_i = effect of diet, $i = 1 - 4$,

e_{ij} = random error.

Where differences were determined, least square means were separated using the Student Neuman-Keuls test (Sokal and Rohlf, 1969).

Repletion data was analyzed by analyses of variance for trial one and trial two in which the data was pooled. The model used was:

$$Y_{ij} = u + d_i + m_j + e_{ij}$$

where:

Y_{ij} = dependent variables,

u = theoretical population mean,

d_i = effect of diet, i = 1 - 4,

m_j = effect of minute, i = 1 -7

e_{ij} = random error.

Where differences were determined in the effect of minutes after repletion, least square means were separated by Student Neuman-Keuls Test. Due to erratic mineral level changes during minutes after repletion, mineral levels were fitted to a trinomial regression on minute. The equation used was:

$$Y = a + b_1 (\text{min.}) + b_2 (\text{Min.}^2) + b_3 (\text{min.}^3),$$

where:

Y = dependent variables,

a = intercept,

min. = minute after repletion,

b_1, b_2, b_3 = the partial regression coefficients for the dependent variables with respect to the independent variable, min., min.^2, min.^3.

CHAPTER IV

RESULTS AND DISCUSSION

I. BALANCE RESULTS

After collection of urine and fecal samples had begun, individual calves contracted diarrhea so the balance period was extended over three weeks into five day collection periods. It was demonstrated by Blaxter and Rook (1954) that mild diarrhea results in a depression of Mg retention. The data indicated that in three calves suffering from diarrhea and fed Mg deficient diets, the mean daily loss of Mg from the body was 117 mg. In the same calves fully recovered, the daily loss was only 42 mg. This increased loss of Mg during diarrhea did not, however, specifically accelerate the depletion of the calf, since the retention of Ca and N was simultaneously depressed. It was apparent that extending the balance period, however, caused difficulties because two calves became severely hypomagnesemic and hypocalcemic. Oral repletion was successful with one calf but not with the other. This contributed to another calf loss and no balance data for that animal. During the second trial, one calf died prior to collection. During the balance phase another calf became severely hypomagnesemic and was found dead one morning after what appeared to be a fatal tetany episode. Only six calves were used from trial three for the balance phase because one calf developed

peritonitis and another contracted chronic diarrhea. Due to these numerous calf losses throughout the experimental period only 19 of the total 24 calves were included in the statistical analyses. The distribution of those calves utilized is shown in Table 6.

Balance results were calculated using mineral intakes determined from composited feed samples and five day averages of urinary and fecal mineral excretions.

Daily Mg balances for the calves are presented in Table 7. Results demonstrated that calves fed diets supplemented in Mg had a higher ($P<.05$) intake of Mg than those not supplemented. Calves fed the Mg deficient diets as well as the adequate Mg plus supplemental K diet excreted less Mg ($P<.05$) in the urine than did calves fed the adequate Mg diet, however, calves fed diet four excreted more ($P<.05$) Mg in the urine than calves fed Mg deficient diets. Blaxter and Rook (1954) found similar results which indicated that the amount of Mg excreted in the urine was always small relative to that excreted in the feces. They found that when the dietary Mg concentration was high, as much as 17 mg out of a total 448 mg consumed, was excreted in the urine, but low intakes were invariably associated with the excretion of only a few mg daily. Rook and Storry (1962) reported that urinary excretion of Mg reflects the nutritional adequancy of the diet, and the transfer of an animal to a diet deficient in Mg was followed by a progressive fall of serum Mg and reduction of urinary Mg excretion until at a threshold value, excretion in the urine ceased. Similar conclusions were

TABLE 6. Distribution of Calves Used for Statistical Analysis of Balance Study

	Treatment Groups			
	1	2	3	4
Trial 1	1	2	2	0
Trial 2	1	2	2	3
Trial 3	1	1	3	1

TABLE 7. Least Square Means of Daily Magnesium Balance in Grams, Calculated From Average Daily Excretion

Component	Treatment			
	Mg Def.	+Mg	+K	+Mg+K
No. calves	3	5	7	4
Intake	.162[a]	2.530[b]	.165[a]	2.093[b]
Urinary excretion	.009[a]	.219[b]	.010[a]	.095[c]
Fecal excretion	.295[a]	1.485[b]	.305[a]	1.439[b]
Balance	-.142[a]	.826[b]	-.150[a]	.559[b]

[a,b,c]Means within a row superscripted with different letters are different ($P<.05$).

drawn by Kemp et al. (1961) and Meyer (1976a). These data agree with that theory. Frye et al. (1975) found that urinary Mg was reduced in animals fed high K rations, which apparently resulted from lowered Mg absorption. It was reported by House and Bird (1975) when a Mg tolerance test was conducted with goats that increased K intake increased the rate of disappearance of Mg from plasma but decreased urinary Mg excretion with the hypothesis that this is due to increased cellular uptake and retention of Mg because of increased cellular K levels. Fontenot et al. (1973) found that the feeding of a high K diet usually decreased urinary Mg which was accompanied by an increase in fecal Mg excretion. Fecal excretion of Mg was lower ($P<.05$) for calves fed Mg deficient diets than calves fed Mg supplemented diets. The feces seem to be the main route of excretion for Mg in calves on all treatments which agrees with other research compiled (Blaxter and Rook, 1954; Kemp et al., 1961). Calves fed the magnesium deficient diets were in a negative balance for Mg while calves fed Mg supplemented diets were in a positive balance.

The daily Ca balance for all trials is presented in Table 8. There were no significant differences across treatments for Ca intake, excretion, or balance with the feces as the major route of excretion for Ca. These results are similar to those demonstrated by Smith (1957) in milk-fed calves. Frye et al. (1975) concluded that high dietary K decreased fecal Ca, however this was not supported by these results from the present study.

TABLE 8. Least Square Means of Daily Calcium Balance in Grams, Calculated from Average Daily Excretion

Component	Treatment			
	Mg Def.	+Mg	+K	+Mg+K
No. of calves	3	5	7	4
Intake	4.794	7.883	5.697	6.996
Urinary excretion	.029	.051	.173	.051
Fecal excretion	3.174	3.768	2.887	3.591
Balance	1.591	4.064	2.637	3.354

Calves fed diets not supplemented in K had a lower ($P<.05$) intake of K than calves fed supplemented K (Table 9). However the calves fed the diet deficient in Mg and supplemented with K consumed a lower ($P<.05$) intake of K than calves fed adequate Mg-supplemented K diets. This was apparently due to anorexia which often accompanies hypomagnesemia. Suttle and Field (1969) found similar results when ewes were fed a similar semi-purified diet as used in this experiment. They indicated that some sheep tended to refuse K-supplemented diets and there was a tendency for refusal to be the highest with Mg deficient diets. Calves fed diets not supplemented in K had a lower ($P<.05$) excretion of urinary K than calves fed diets supplemented in K. This is logical since the urine is the main route of excretion for excess K which agree with work conducted by House and VanCampen (1971). Total urine output was increased for calves fed the diets high in K which was partly due to increased water intake. Fecal excretion of K did not differ across treatments which contradicts the data presented by Fyre et al. (1975) that fecal K was decreased as dietary Mg levels increased in both low and high K rations. The balance results indicated that all calves were in a positive balance for K, however, calves fed the Mg-deficient diet retained less ($P<.05$) than calves fed adequate Mg plus supplemented potassium. Calves fed the other two rations did not differ from either the Mg-deficient or adequate Mg-supplemented K diets. These differences are more than likely due to the intake of K by the individual calves not an effect on K absorption

TABLE 9. Least Square Means of Daily Potassium Balance in Grams, Calculated from Average Daily Excretion

Component	Treatment			
	Mg Def.	+Mg	+K	+Mg+K
No. of calves	3	5	7	4
Intake	8.06[a]	11.89[a]	41.42[b]	57.58[c]
Urinary excretion	7.62[a]	8.45[a]	30.36[b]	43.92[b]
Fecal excretion	.43	.46	.66	.73
Balance	.01[a]	2.98[ab]	10.40[ab]	12.93[b]

[a,b,c]Means within a row superscripted with different letters are different ($P<.05$).

or retention. Greene et al. (1981) concluded that level of dietary Mg did not affect K absorption. The data presented here supports that conclusion.

II. REPLETION RESULTS

During trial one there was an increased occurrence of hypomagnesemic tetany. This resulted in the administration of preliminary oral repletions with 50 ml of 30% $MgCl_2 \cdot 6H_2O$ solution in which plasma samples were obtained and analyzed for Mg, Ca, and K.

During the balance period a calf went into a severe tetany seizure at the evening feeding. The calf was successfully orally repleted with the $MgCl_2$ solution and plasma samples were collected over a three hour period. The day before this episode plasma Mg level of the animal was .25 mg/dl and at time of the baseline sample it was .51 mg/dl. This supports the theory that during a tetany episode plasma Mg levels may very well increase. The final 180 minute sample obtained analyzed to be only .84 mg/dl which is still considered severely hypomagnesemic. The plasma K level of this calf was unusually high which was probably due to the increased K intake by that animal. Results of this repletion are shown in Table 10. Eighteen days later the calf had another tetany episode in which the animal was also severely hypocalcemic. Hypocalcemia often accompanies chronic low plasma Mg levels as shown by Parr (1957). The tetanic episode seemed more

TABLE 10. Effect of Oral $MgCl_2 \cdot 6H_2O$ Administration on Plasma Mineral Levels of Calf on 11/19/81

Minutes Post Dosing	Plasma Levels, mg/dl		
	Mg	Ca	K
0	0.51	8.35	27.63
5	0.66	7.50	22.59
15	*	*	*
30	0.58	7.35	21.09
60	0.51	7.36	20.18
120	0.64	7.73	19.12
180	0.84	7.72	19.65

*Unable to obtain sample.

severe than that due to just low plasma Mg levels and it took longer for the animal to recover from the seizure. In fact this calf did not recover until between the 120 and 180 minute blood samples. It was also observed that the calf had very cold extremities as compared to hypomagnesemic calves with normal plasma Ca. Results of this repletion are shown in Table 11.

As shown in the first oral repletion of this calf, the administration of 30% $MgCl_2 \cdot 6H_2O$ was sufficient enough to relieve the clinical signs of the tetany, however did not increase the Mg or Ca in sufficient amounts to raise the plasma levels to a normal range. An attempt was made to obtain CSF samples, however it was unsuccessful. Approximately one week later another tetany episode resulted, however the calf was terminated in order to collect tissue samples. During tissue collection it was observed that the cisterna magna and spinal area was practically devoid of CSF. No explanation can be offered why this occurred, but dehydration may have been a contributing factor.

Another calf that was also hypomagnesemic and hypocalcemic was found one morning in severe tetanic convulsions similar to those reported above. Repletion was totally unsuccessful and within 24 hours the animal became comatose and was terminated.

TABLE 11. Effect of Oral $MgCl_2 \cdot 6H_2O$ Administration on Plasma Mineral Levels of Calf on 12/7/83

Minutes Post Dosing	Plasma Levels, mg/dl		
	Mg	Ca	K
0	0.51	5.98	24.53
5	0.64	5.96	23.96
15	0.68	6.21	21.13
30	0.74	6.27	21.93
60	0.58	6.09	22.14
120	0.52	6.08	18.09
180	0.65	6.09	19.17

Repletion data was obtained from 19 of the total 24 calves due to calf losses previously reported. Analysis of variance indicated there was no date effect therefore all data was pooled from trial one and trial two; however, calves from trial three were repleted with 100 ml of 30% $MgCl_2 \cdot 6H_2O$ as opposed to 50 ml to study the effect of volume of the rumen on the data collected. Number of calves available did not suffice for an analysis of variance for trial three; therefore, means from trial one and trial two were pooled and compared graphically to means from trial three. Due to erratic mineral level changes during the three hour repletion period plots of regression curves were utilized.

Results from pooled trial one and two indicated that plasma Mg of calves fed the Mg deficient diet increased ($P<.05$) from a baseline value of .44 mg/dl to .60 mg/dl at 120 minutes and .62 mg/dl at 180 minutes after repletion with 50 ml of 30% $MgCl_2 \cdot 6H_2O$. Oral Mg solutions had no significant effect on plasma Mg in calves on the other diets (Figure 1).

Plasma K levels increased ($P<.01$) in calves fed the Mg deficient diet over time, however, not at a consistent rate. Plasma K remained the same in calves fed the diet adequate in Mg. The Mg deficient plus supplemental K fed calves had a decrease ($P<.01$) in plasma K over time from a baseline to 180 minute value of 22.35 to 18.40 mg/dl, respectively while the calves fed the diet adequate in Mg plus supplemental K increased ($P<.01$) from a beginning plasma level of 17.59 mg/dl to 19.93 mg/dl at 120 minutes

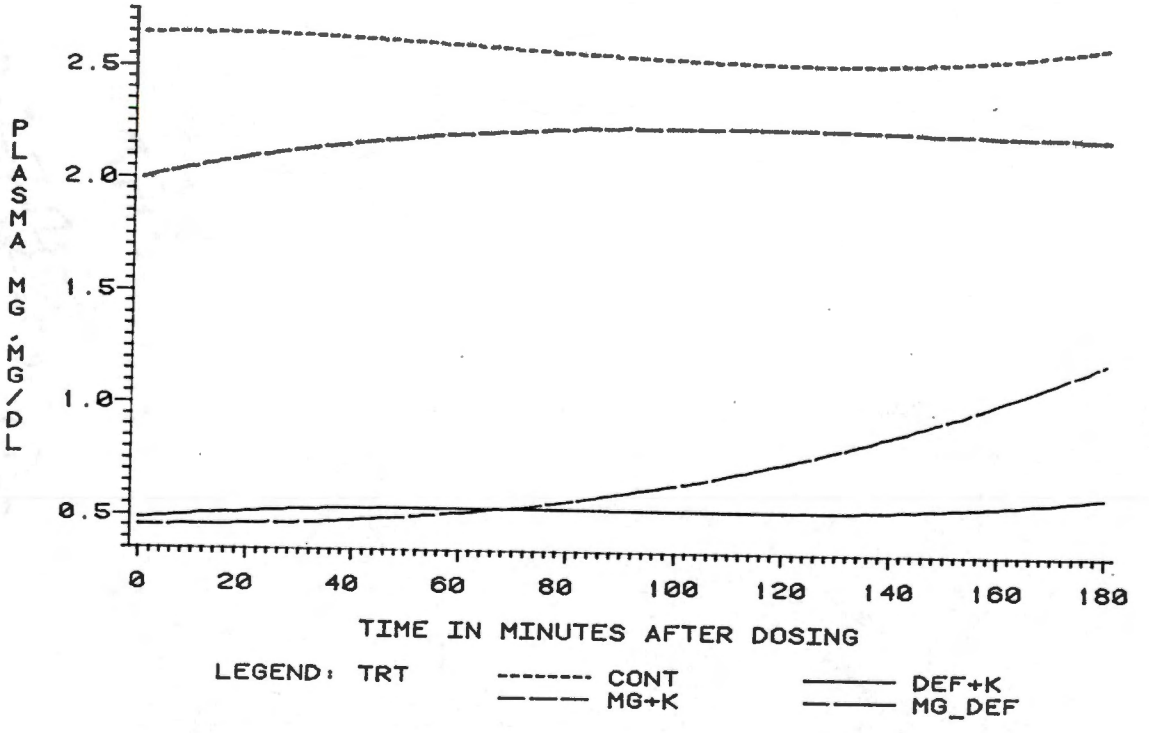

FIGURE 1. Regression curves for plasma Mg in hypomagnesemic or normomagnesemic calves fed normal or excess K after oral dosing with 50 ml of 30% $MgCl_2 \cdot 6H_2O$.

and to 20.33 mg/dl at 180 minutes (Figure 2). The results of a Mg tolerance test in goats conducted by House and Bird (1975) found that plasma K levels decreased temporarily following Mg loading. They indicated that if cellular Mg levels increased temporarily after Mg loading, this may have initiated a transitory shift of K from plasma to cells. Similar responses in plasma K to intravenous infusions of Mg have been observed by Bergman and Sellers (1953) in dairy calves. This could certainly be an explanation for the decreased plasma K after repletion for calves fed a Mg deficient diet supplemented with K, however plasma K levels increased in calves fed the diet adequate in Mg and supplemental K. Tissue uptake of the crucial Mg in the deficient calves possibly caused a transitory shift of the K more rapidly than calves not depleted in Mg. This could be supported by work conducted by McAleese et al. (1961) which indicated that deficient animals cleared plasma ^{28}Mg more rapidly and had a greater tissue uptake of ^{28}Mg than control animals. Another plausible explanation is that calves fed the adequate Mg diets consumed more feed and thus more K (65.25 g/day) than calves fed the Mg deficient diet (44.55 g/day). This would alter plasma K between the diets.

In calves fed the Mg deficient diet and calves fed the diet adequate in Mg, CSF Mg remained constant over time. Calves fed the Mg deficient diet supplemented with K had a decrease ($P<.05$) in CSF Mg from a beginning value of 1.76 mg/dl to a 180 minute level of 1.14 mg/dl, however the calves fed the diet adequate in

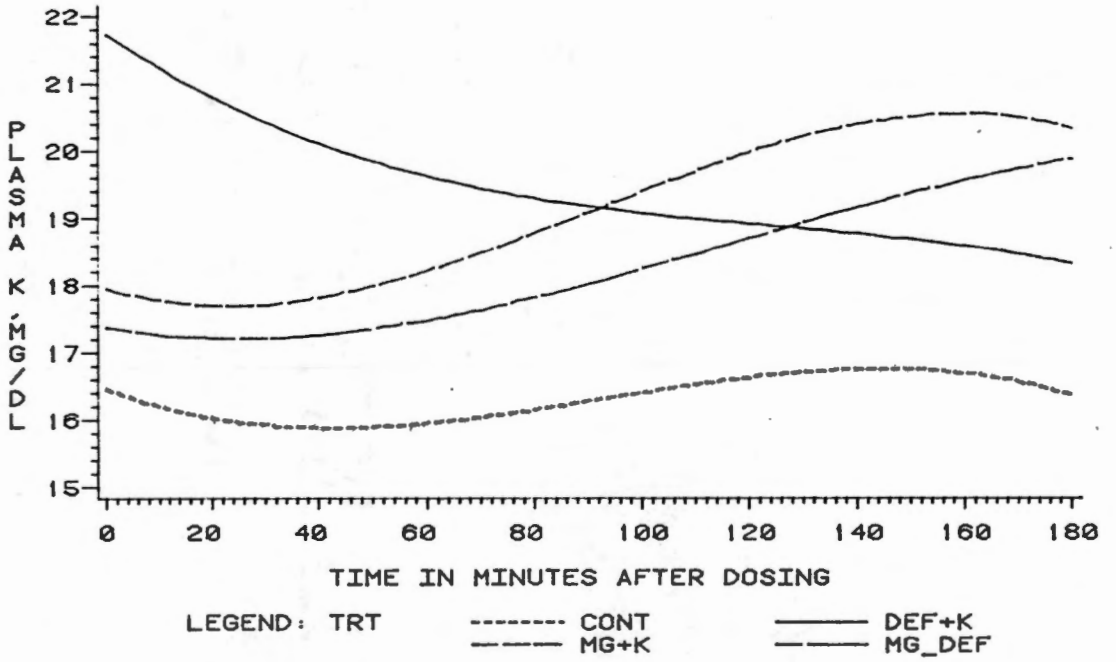

FIGURE 2. Regression curves for plasma K in hypomagnesemic or normomagnesemic calves fed normal or excess K after oral dosing with 50 ml of 30% $MgCl_2 \cdot 6H_2O$.

Mg and supplemented with K had a baseline value of 2.02 mg/dl that remained fairly constant (Figure 3).

Administration of 30% $MgCl_2 \cdot 6H_2O$ had no effect on CSF K in calves fed either Mg deficient or adequate diets, with or without supplemental K. This was true for the calves fed diets supplemented with K also. However, calves fed a diet deficient in Mg and supplemented with K had a trend in increasing CSF K with oral dosing from a beginning level of 13.37 to a 180 minute level of 15.24 mg/dl (Figure 4).

Effects of amount of $MgCl_2 \cdot 6H_2O$ (50 vs 100 ml of 30% solution) on plasma and CSF minerals were compared. Due to cell numbers among treatments only LS means were compared. Plasma Mg in calves fed the Mg deficient diet increased from .56 to .91 mg/dl 180 minutes after drenching with 100 ml of 30% $MgCl_2 \cdot 6H_2O$ compared to an increase from .44 to .62 mg/dl when drenched with 50 ml. In calves dosed with 50 ml CSF Mg fluctuated; however, there was a trend in calves dosed with 100 ml to increase from the baseline value of 1.43 to a 180 minute value of 1.55 mg/dl (Figure 5). Calves fed the diet adequate in Mg had plasma Mg which remained fairly constant over time for the 50 ml volume, while in calves dosed with 100 ml there was a trend to increase by 180 minutes after dosing. No CSF Mg was obtained for the calf repleted with 100 ml volume of $MgCl_2 \cdot 6H_2O$; therefore, no comparison was made for this diet (Figure 6). The Mg deficient plus supplemental K fed calves had plasma Mg remaining linear at either volume repleted. Repletion

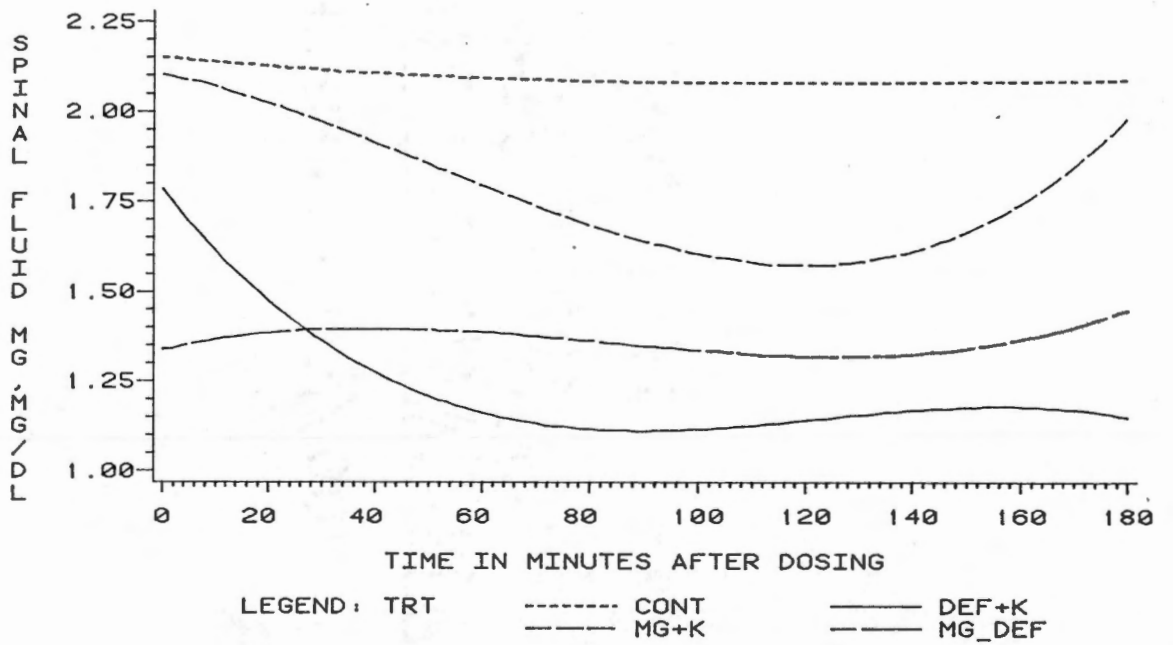

FIGURE 3. Regression curves for CSF Mg in hypomagnesemic or normomagnesemic calves fed normal or excess K after oral dosing with 50 ml of 30% $MgCl_2 \cdot 6H_2O$.

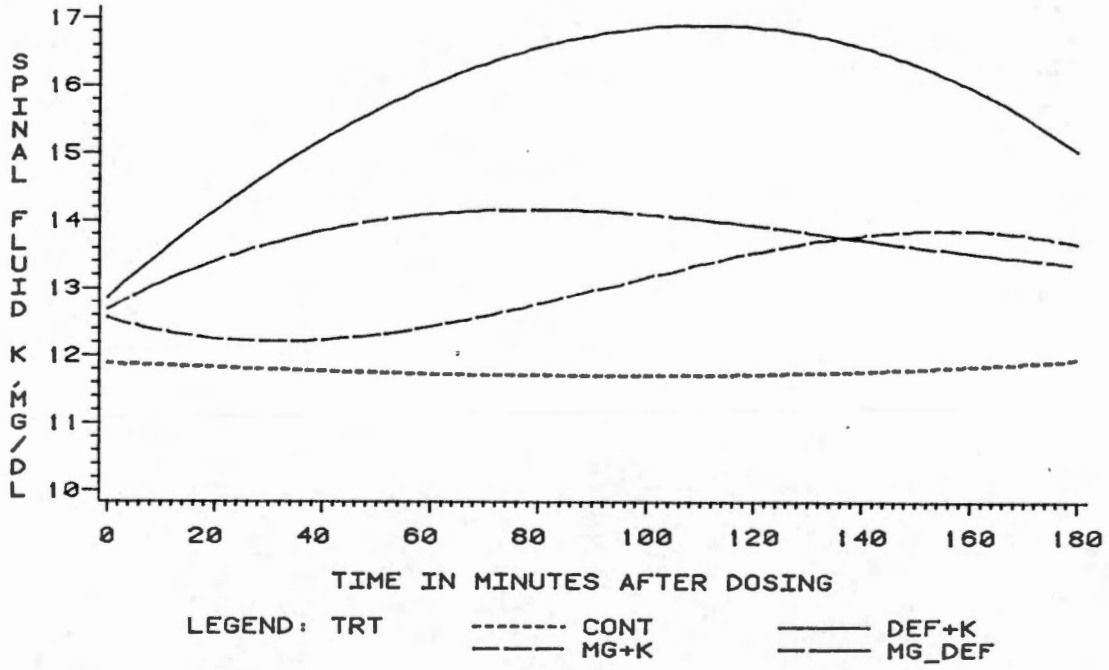

FIGURE 4. Regression curves for CSF K in hypomagnesemic or normomagnesemic calves fed normal or excess K after oral dosing with 50 ml of 30% $MgCl_2 \cdot 6H_2O$.

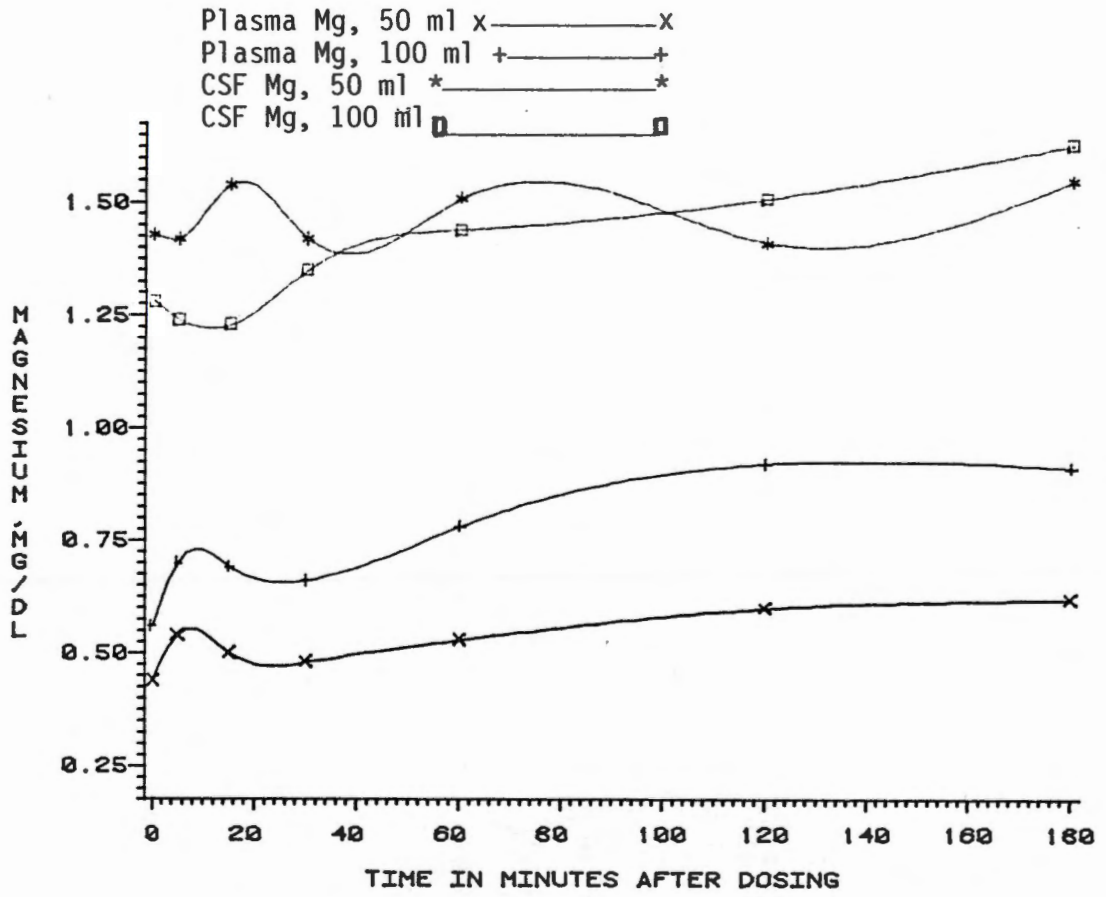

FIGURE 5. Comparison of repletion with 50 or 100 ml of 30% $MgCl_2 \cdot 6H_2O$ on plasma and CSF Mg of calves fed Mg deficient diets.

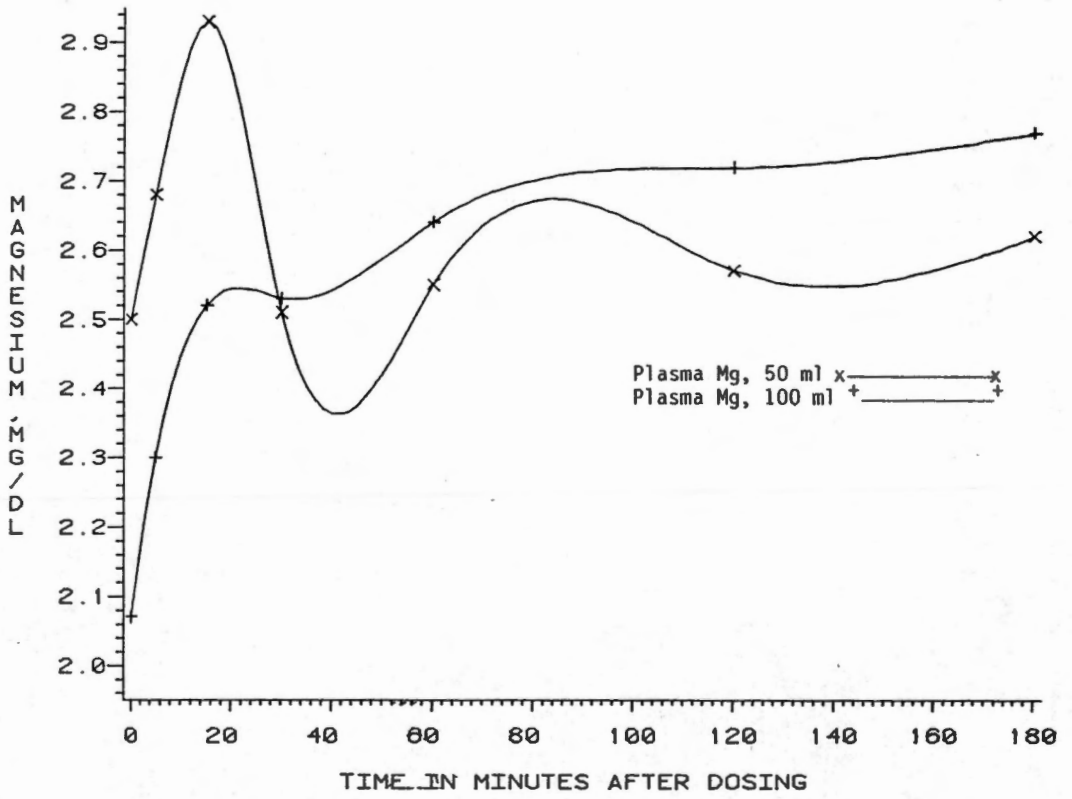

FIGURE 6. Comparison of repletion with 50 or 100 ml of 30% $MgCl_2 \cdot 6H_2O$ on plasma Mg of calves fed adequate Mg diets.

plus supplemental K fed calves had plasma Mg remaining linear at either volume repleted. Repletion of CSF Mg at the 50 ml volume decreased ($P<.01$) as previously indicated, however the 100 ml volume tended to increase CSF Mg levels (Figure 7). There was a trend for plasma Mg to increase by .72 mg/dl in calves dosed with 100 ml but to remain constant in calves dosed with 50 ml when the adequate Mg plus supplemental K diet was fed. This oral repletion with 100 ml gave very similar results to those obtained by rectal infusions indicating that more than 50 ml of $MgCl_2 \cdot 6H_2O$ should be administered with oral drenching. Repletion of CSF Mg remained fairly constant over time with a 50 ml dosage, however the 100 ml dosage fluctuated over the 180 minute period (Figure 8).

Plasma K increased ($P<.01$) as previously indicated in calves fed the Mg deficient diet with a 50 ml repletion, however it remained fairly constant in calves repleted with 100 ml of $MgCl_2 \cdot H_2O$. At both repletion volumes CSF K remained constant (Figure 9). Plasma K of calves fed adequate Mg remained unchanged for 180 minutes after dosing with 50 ml; however increased at 60 minutes then returned close to baseline level at 120 minutes after dosing with 100 ml (Figure 10). Calves fed the Mg deficient diet plus supplemental K repleted with 50 ml decreased ($P<.01$) from a baseline value of 22.35 to a 180 minute value of 18.40 mg/dl of K, while in calves repleted with 100 ml there was a trend to increase and then return close to the baseline value

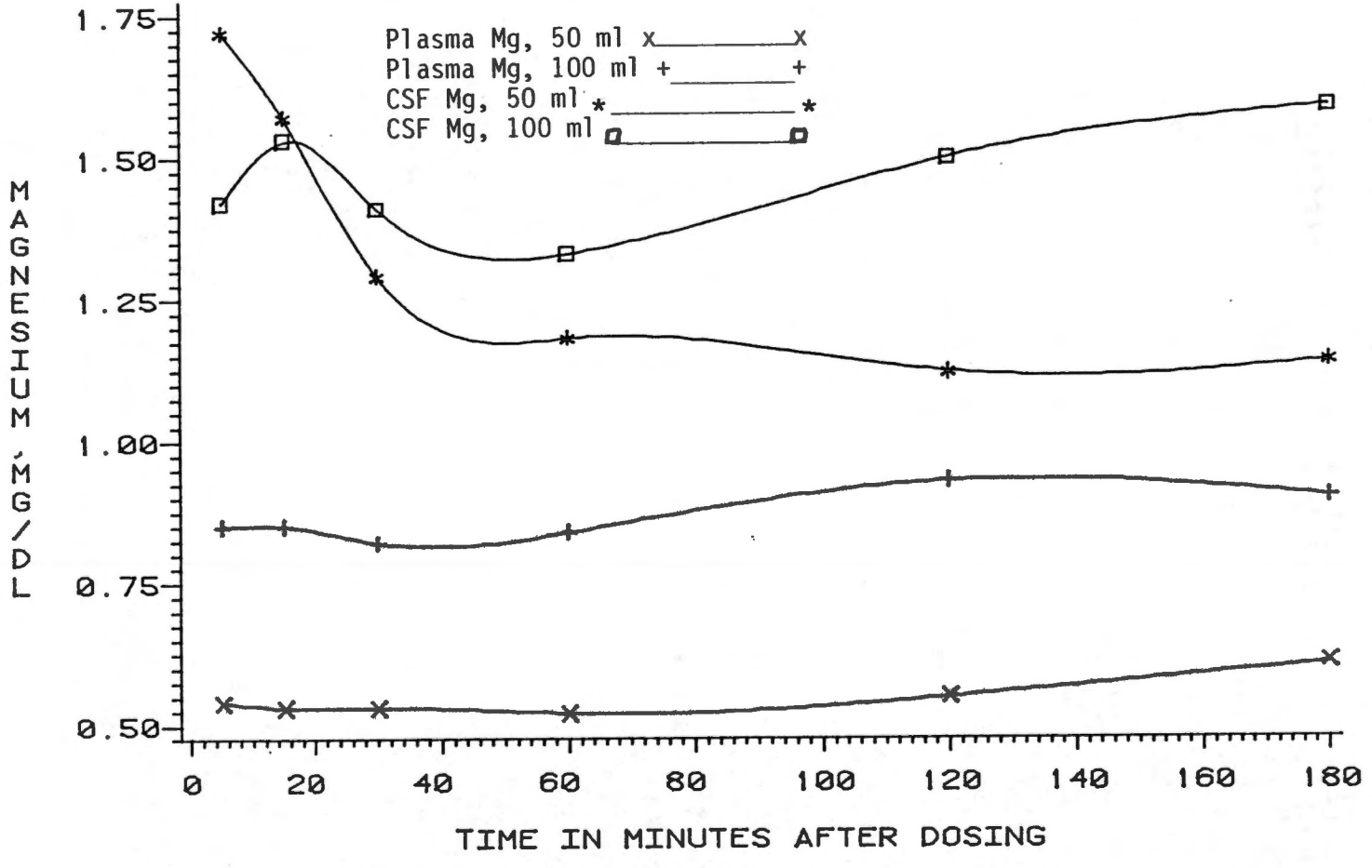

FIGURE 7. Comparison of repletion with 50 or 100 ml of 30% $MgCl_2 \cdot 6H_2O$ on plasma and CSF Mg fed Mg deficient plus supplemental K diets.

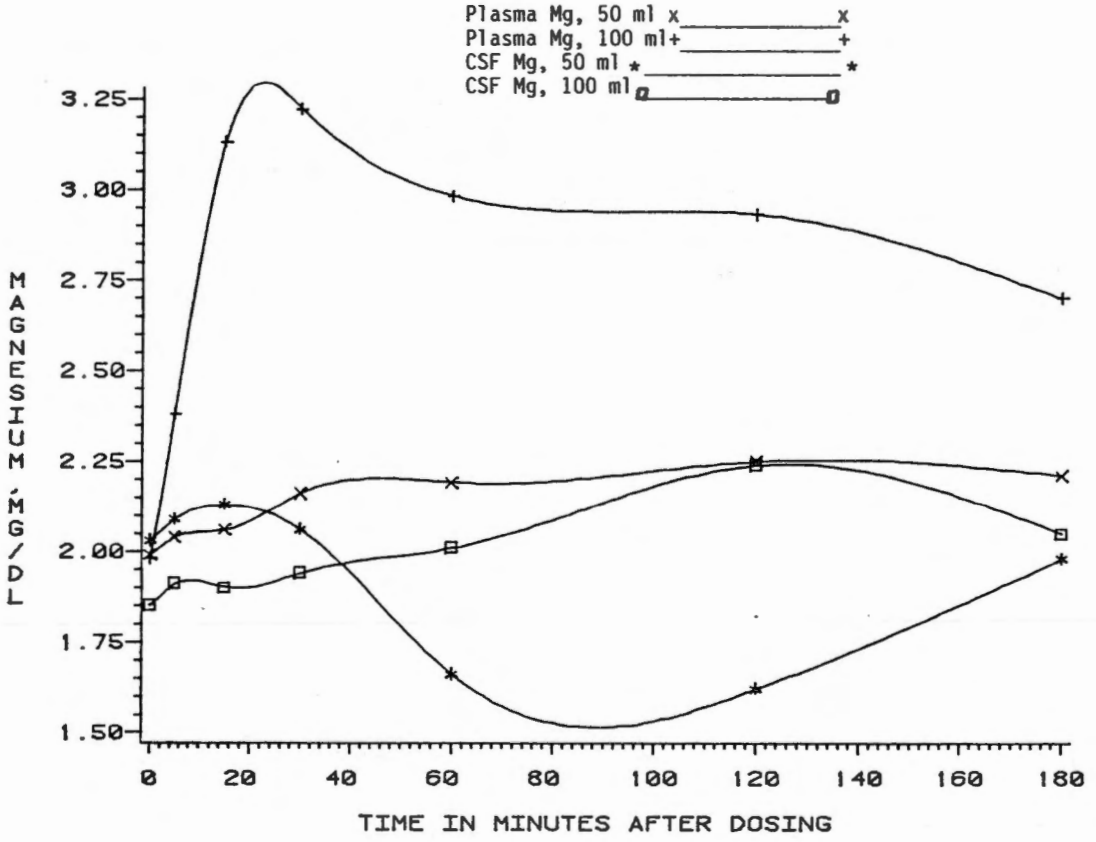

FIGURE 8. Comparison of repletion with 50 or 100 ml of 30% $MgCl_2 \cdot 6H_2O$ on plasma and CSF Mg of calves fed Mg adequate plus supplemental K diets.

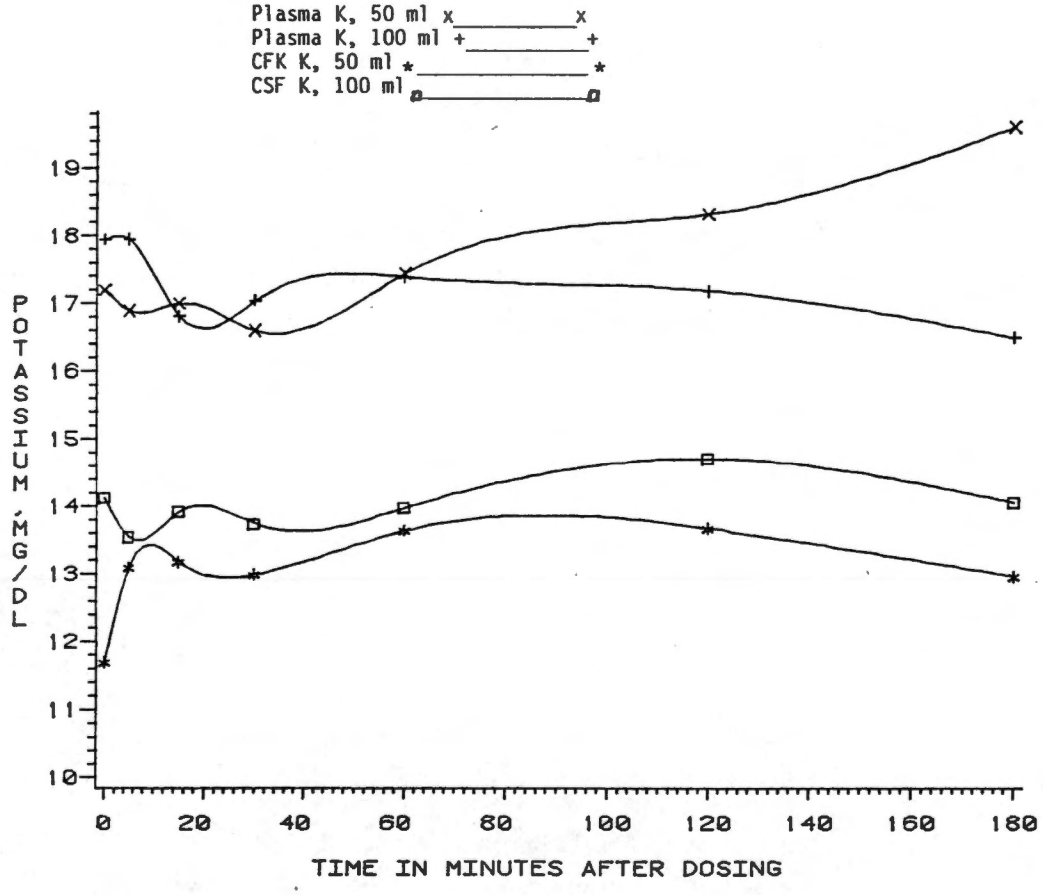

FIGURE 9. Comparison of repletion with 50 or 100 ml of 30% $MgCl_2 \cdot 6H_2O$ on plasma and CSF K of calves fed Mg deficient diets.

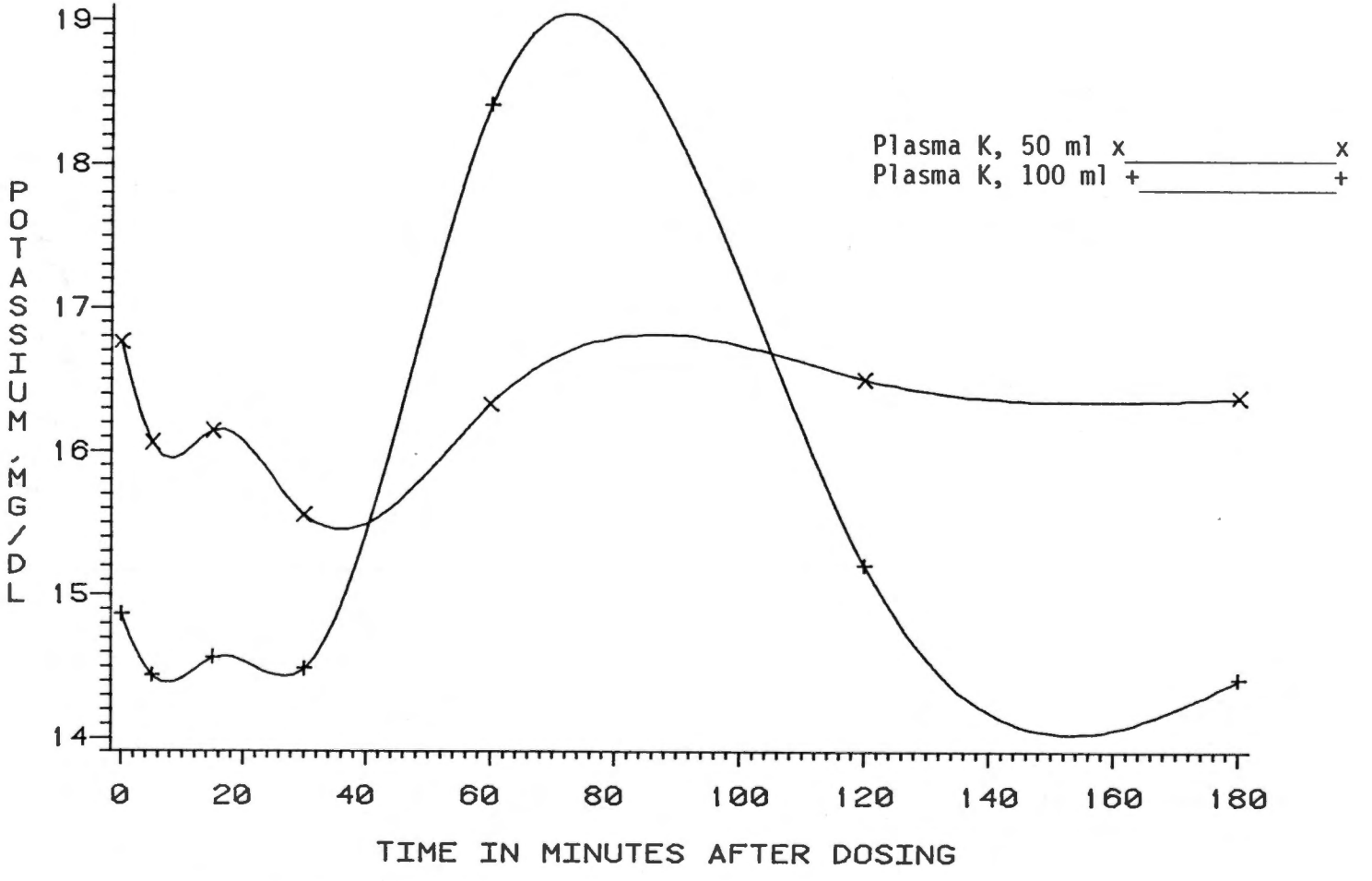

FIGURE 10. Comparison of repletion with 50 or 100 ml of 30% $MgCl_2 \cdot 6H_2O$ on plasma K of calves fed Mg adequate diets.

of 18.20 at 180 minutes. There was a trend for CSF K to increase in calves dosed with 50 ml, while calves dosed with 100 ml remained fairly constant (Figure 11). Calves fed the adequate Mg with supplemental K diet tended to increase in plasma K when dosed with 50 ml of $MgCl_2 \cdot 6H_2O$ solution. Calves dosed with 100 ml increased from a baseline value of 16.82 to a 120 minute value of 20.94 then decreasing to 18.69 mg/dl. In calves dosed with 50 ml, CSF K remained linear while there was a trend to increase in calves dosed with 100 ml solutions of $MgCl_2:6H_2O$ (Figure 12). Plasma and CSF Ca remained unchanged at either 50 or 100 ml dosage.

There are no consistent trends to increase plasma or CSF Mg by increasing the volume administered to 100 ml. It is apparent that the effects of oral repletion with 50 or 100 ml are minimal in comparison with a highly significant response in plasma and CSF Mg from previous work conducted with rectal infusions. Reynolds (1981) indicated that a rectal infusion of 50 ml 30% $MgCl_2 \cdot 6H_2O$ caused a rapid increase in plasma Mg levels and increased subnormal CSF Mg levels within 30 minutes after administration to young calves. Bell et al. (1977) indicated that giving 60 g of $MgCl_2 \cdot 6H_2O$ in solution as a rectal infusion to beef cows increased the plasma Mg from a value of .65 mg/dl to 2.22 mg/dl within 20 minutes. Littledike and Cox (1979) indicated that the colonic transport of Mg ion requires a simultaneous transport of an anion. Thus $MgCl_2 \cdot 6H_2O$ is highly successful as a rectal infusion because of the chloride ion present.

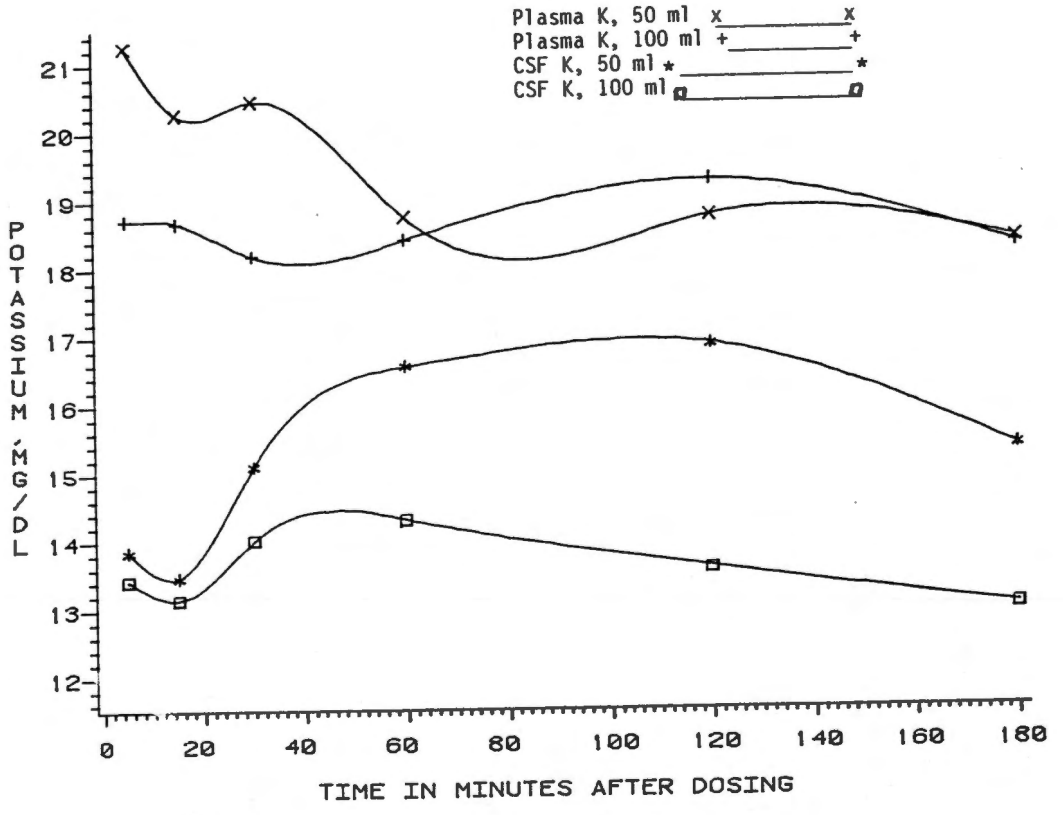

FIGURE 11. Comparison of repletion with 50 or 100 ml of 30% $MgCl_2 \cdot 6H_2O$ on plasma and CSF K of calves fed Mg deficient plus supplemental K diets.

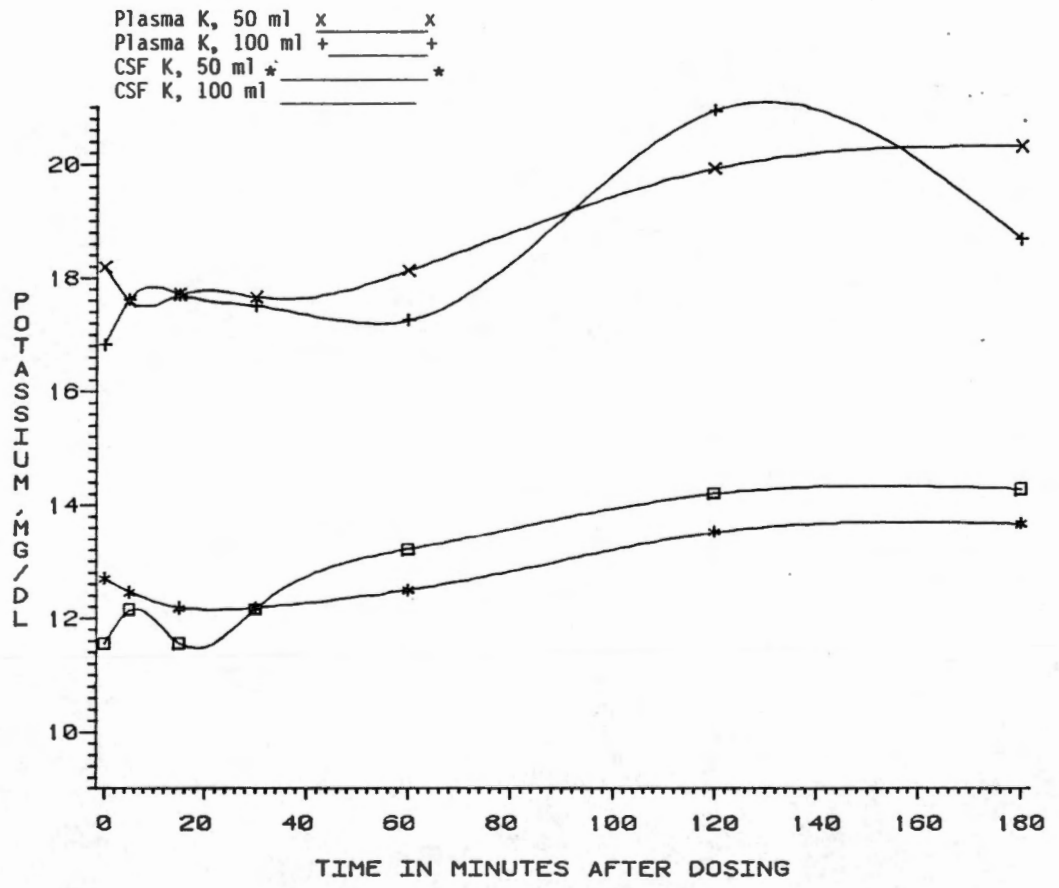

FIGURE 12. Comparison of repletion with 50 or 100 ml of 30% $MgCl_2 \cdot 6H_2O$ on plasma and CSF K of calves fed Mg adequate plus supplemental K diets.

Explanations for these differences between oral and rectal administration of Mg could be due to various factors. The anesthesia used to facilitate placement of CSF catheters into the cisterna magna may have a significant effect on motility of the rumen during the repletion. Reynolds (1981) found anesthesia to have no effect on absorption of Mg from a rectal infusion.

Van Soest (1982) indicated that the rumen volume is approximately 9 to 13% of body weight in cattle while the colon and rectum comprises only .8 to 1.5% of body weight. He indicated that calves at 3 months of age have rumen development three fourths of that of adult cattle. With this in mind the rumen volume is approximately 9 to 10 times larger than the rectal volume. This dilution factor could present some problems when using an oral drench of 30% $MgCl_2 \cdot 6H_2O$ as a treatment for hypomagnesemia. Smith (1959c) indicated that Mg in a concentration up to 8 mg/100 ml in the rumen fluid did not appear to be absorbed through the rumen wall in calves which contradicts work that has been conducted with mature sheep.

Fitt et al. (1972) indicated in a study using cell walls of specific rumen bacteria that these microorganisms are capable of binding Mg and the extent of binding is increased by degradation of the cell wall. The presence of bound Mg in the cell wall is believed to be essential for maintenance of membrane function. They hypothesized that it is possible that the intervention of the rumen microbial population is largely responsible for this reduced

availability especially when Mg is critically low. This agrees with Meyer (1976a) who indicated that the binding of Mg by bacterial proteins may depress its solubility. As shown in Figure 8, page 80, the increase in plasma Mg was similar to that of rectal infusions. Possibly the microbes reached a saturation point which increased the available Mg for absorption. A combination of anesthesia effects, rumen volume, and microbial populations of the rumen probably played a key role in reducing the effectiveness of oral repletions with 50 or 100 ml of 30% $MgCl_2 \cdot 6H_2O$

III. TISSUE RESULTS

As earlier reported, numerous calf losses were encountered, however only one calf was found dead as a result of tetanic convulsions. Death was attributed to cardiac arrest. The pathology showed fresh ecchymotic and purpuric hemorrhages on the surface of the lungs as well as inside the lung tissue. Subepicardial petechial and ecchymotic hemorrhages on the heart and interior surfaces of the ventricles were also noted. Data compiled by other researchers have shown extensive hemorrhages principally in the pleural cavity coupled with acute congestion of internal organs. Hemorrhagic lesions were very marked on the epi- and endocardium, throughout the cardiovascular system, the thymus, lungs, and muscles. The heart valves were usually reddened and sometimes edematous (Moore et al., 1936; Thomas, 1959; Haggard et al., 1978). Similar results were demonstrated in this experiment as that found by

Miller and Schneider (1981). They reproduced vascular lesions in sheep when injecting a collagen substance. It was theorized that these vascular lesions cause platelet aggregation and may be a significant mortality risk factor in animals.

Blaxter et al. (1954) indicated that these lesions were absent in hypomagnesemic slaughtered calves. Results here were similar. Three calves were terminated while in tetanic convulsions, however no lesions appeared to be present. Death with hypomagnesemia occurs probably due to dysfunction of the cardiac area producing lesions which supports the platelet aggregation theory.

Tissue data was collected from 18 of the 24 calves and pooled by treatment. The distribtution of calves utilized for tissue analysis is shown in Table 12. Analysis of variance indicated that there were no significant changes in Mg concentration across treatments for heart, brain, lung, liver, spleen, skeletal muscle, or kidney tissue.

Similar to data indicated by Rook and Storry (1962) the Mg content of the soft tissues varied widely from tissue to tissue and among individual animals. Most research conducted (Blaxter et al., 1954; Wilson, 1964; Littledike and Cox, 1979; Miller et al., 1981) have drawn the conclusion that the Mg concentration of the soft tissues does not deplete in hypomagnesemic animals as compared to normal animals. Similar results are shown in Table 13. In calves fed diets adequate in Mg with supplemental K, the lung Ca was higher ($P<.05$) at a level of .48 mg/g dry basis compared to the lungs of calves on other treatments which ranged from .33

TABLE 12. Distribution of Calves for Statistical Analysis of Tissues

	Treatment groups			
	1	2	3	4
Trial 1	1	0	2	0
Trial 2	1	2	1	4
Trial 3	1	1	3	2

TABLE 13. Least Square Means of Organ Minerals in mg/gram Dry Basis

Treatment	Minerals		
	Magnesium	Calcium	Potassium
	---------- Heart ----------		
Mg deficient	.85	.25	10.53
+Mg	.97	.19	12.99
+K	.87	.21	12.79
+Mg+K	.89	.18	10.82
	---------- Liver ----------		
Mg deficient	.64	.20	10.36
+Mg	.58	.16	11.42
+K	.62	.26	11.17
+Mg+K	.62	.18	10.22
	---------- Brain ----------		
Mg deficient	.66	.30	15.69
+Mg	.59	.30	16.21
+K	.59	.38	15.54
+Mg+K	.52	.25	13.20
	---------- Spleen ----------		
Mg deficient	.52	.16	11.11
+Mg	.52	.22	11.00
+K	.62	.24	13.23
+Mg+K	.56	.19	9.11
	---------- Kidney ----------		
Mg deficient	.65	.27	11.03
+Mg	.82	.29	12.20
+K	.62	.35	11.66
+Mg+K	.65	.38	11.24
	---------- Lung ----------		
Mg deficient	.54	.34[a]	11.88
+Mg	.54	.37[a]	11.31
+K	.45	.33[a]	9.93
+Mg+K	.55	.48[b]	10.22

[a,b]Means within a column superscripted with different letters are different ($P<.05$).

to .37 mg/g dry basis. This was attributed to a calf on the supplemental K diet having lung tissue analyzing .60 mg Ca/g on dry basis. Ullrey (1977) indicated some of the analytical problems associated with tissue analysis which were very much a factor in the analyses represented here such as contamination and moisture loss during storage which are probably the two most frequent factors in error of tissue sampling and analysis. No changes across treatments in Ca concentration or K concentration were noted.

Depletion of bone Mg in hypomagnesemic animals has been thoroughly demonstrated by numerous researchers (Blaxter et al., 1954; Parr, 1957; Miller et al., 1981). It was concluded by Wilson (1964) that in young rats and calves on Mg deficient diets there was a fall in the concentration of bone Mg by 30%. Smith concluded that the Mg content of bone decreases as the age of a calf increases and 60 to 80% of the Mg retained by a normal calf is laid down in bone.

Results indicated by the tissue data presented here were similar. Rib Mg was lower ($P<.05$) for calves fed diets not supplemented in Mg, in fact there was a similar reduction as Wilson (1964) indicated of over 30%. K also had an effect on the rib mineral concentrations. Calves fed a Mg deficient diet or adequate Mg plus K diet had less ($P<.05$) rib K than calves fed a Mg deficient plus supplemented K diet. Calves fed an adequate Mg diet did not differ in rib Mg from the other treatments (Table 14). Rib mineral levels of Ca did not differ across treatments.

TABLE 14. Least Square Means of Tissue Minerals in mg/gram Dry Basis

Treatment	Minerals		
	Magnesium	Calcium	Potassium
	---------- Skeletal Muscle ---------		
Mg deficient	.91	.12	14.78
+Mg	.80	.19	13.27
+K	.89	.17	15.32
+Mg+K	.79	.19	12.64
	---------- Rib ----------		
Mg deficient	2.71[a]	201.52	1.23[a]
+Mg	4.27[b]	197.47	1.49[a,b]
+K	2.23[a]	194.39	1.98[b]
+Mg+K	3.88[b]	193.38	1.20[b]

[a,b]Means within a column superscripted with different letters are different ($P<.05$).

Spleen K levels fluctuated from approximately 6 mg/g to 16 mg/g, however no differences in levels across treatments were obtained. These differences were probably due to the number of red blood cells (RBC) present within the organ or genetic variation among animals. Bell et al. (1978) indicated that RBC K is affected by genetrics and age of an animal which may be a possible explanation for this variation in concentration.

CHAPTER V

SUMMARY

Young Holstein bull calves were utilized in this study to better understand the etiology of hypomagnesemia. All calves were fed one of four semi-purified diets which contained either adequate or deficient Mg with or without supplemental K. Three separate balance studies were conducted in which intake, feces, and urine were measured and aliquots were obtained for analyses. Immediately following the balance period each calf was orally drenched with 50 or 100 ml of 30% $MgCl_2 \cdot 6H_2O$ solution. Tissue samples were collected 48 hours post-dosing and included lung, heart, brain, spleen, liver, skeletal muscle, rib, and kidney.

Calves fed diets supplemented in Mg had higher ($P<.05$) Mg intake, fecal excretion, and retention than those calves fed Mg deficient diets. Calves fed Mg deficient, Mg deficient plus supplemental K, and the adequate Mg plus supplemental K excreted .009, .010, and .095 g per day of Mg in the urine, respectively compared to .219 g per day of Mg for calves fed the diet adequate in Mg. Calves fed diets not supplemented in K had a lower ($P<.05$) K level of intake and urinary excretion. Fecal excretion of K remained unchanged across treatments. Calves fed the diet adequate in Mg plus supplemental K had a higher ($P<.05$) K balance than calves fed the Mg deficient diet. Balances for Ca did not differ across treatments.

Concentrations of Mg in plasma of calves fed the Mg deficient diet increased from a baseline level of .44 mg/dl to .62 mg/dl 180 minutes after repletion with 50 ml of 30% $MgCl_2 \cdot 6H_2O$ solution. In contrast to previous results when 15 g Mg in 50 ml were administered rectally, the same amount of Mg given orally to calves on other dietary treatments did not increase plasma Mg. Twice as much Mg (30 g in 100 ml) given orally to calves fed adequate Mg but excess K increased in plasma Mg similarly to previous experiments in which 15 g Mg in 50 ml was given rectally. Concentrations of Mg in CSF decreased ($P<.05$) from a baseline of 1.76 mg/dl to 1.14 mg/dl at 180 minutes after oral dosing with Mg but remained fairly constant over the 180 minutes in calves on other treatments.

Concentrations of Mg in brain, heart, liver, spleen, skeletal muscle, kidney, or lung were not influenced by dietary intakes of Mg or K. There was a reduction of over 30% ($P<.05$) in rib Mg of calves fed no supplemental Mg when compared to calves fed Mg supplemental diets.

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