I. Introduction

Milk fever is a metabolic disorder in which the homeostatic mechanisms fail to maintain plasma calcium concentration at normal levels (~ 9-10 mg / 100 ml). This can cause severe hypocalcemia, paresis, recumbency, and eventually death of the cow (Fig. 1). Nearly all cases occur within 3 days of parturition (J. M. Payne 1989), especially in old cows.

In pregnant dry cows, the calcium metabolism is in balance. This means that the input of calcium to the blood from the intestine and bones equals the output of plasma calcium into the bone, feces, urine and fetus (5-9 gr./day). On the other hand, at delivery the exchange into the fetus becomes zero, but the output to colostrum is of approximately 15-25 gr./day. This is why it is very important for dairy cows to get to parturition with calcium regulating hormones (Parathyroid hormone and vitamin D) activated, as this sudden calcium output with colostrum cannot be compensated by normal feeding practices (Fig. 2).

II. Effects of Parathyroid Hormone and Vitamin D in Plasma Calcium regulation

PTH and 1,25 dihydroxy vitamin D activity are markedly and inversely dependent upon dietary calcium levels (Fig. 3). In response to low dietary calcium, PTH hormone stimulates calcium resorption from the bones, and indirectly stimulates calcium absorption from the intestine by activating 1,25 dihydroxy vitamin D production in the kidney (Fig. 4). This activated form of vitamin D plays an important role not only in calcium resorption from bone, but also and most important, in calcium absorption from the intestine, as mentioned before.
In the book “Recent Advances in Animal Nutrition” (1991), Block refers to both passive and active absorption of intestinal calcium. It has been demonstrated that plasma calcium deficiency induces active calcium transport from the intestine by the active form of vitamin D (Block 1991, Goff et. Al. 1995, DeLuca 1979, Westerhuis 1974). The most active site of calcium absorption in response to vitamin D is the duodenum (DeLuca 1979), although he also mentions that vitamin D stimulates the transport of calcium throughout the small and to some extent large intestine. 1,25(OH)₂D₃ is transported in the plasma by a transport protein (carrier), which transfers this 1,25(OH)₂D₃ to the villus cell where it becomes associated by a vitamin D receptor protein. After this, the receptor protein is modified and enters the nucleus, where transcription of specific DNA and protein synthesis takes place, in response to the 1,25(OH)₂D₃. This new protein (calcium binding protein) gets to the brush border membrane, permitting the calcium to get into the cell, where it is either packaged in vesicular membranes or is accepted as calcium phosphate granules in the mitochondria (DeLuca). Calcium is then transferred to the baso-lateral membrane where it is expelled to the ECF against an electrochemical gradient, involving two mechanisms according to Castro in “Gastrointestinal Physiology by Johnson” (Fig. 5), and by one system according to DeLuca’s “Vitamin D: Metabolism and Function” (Fig. 6). In the first case, Castro mentions the Calcium-ATPase as the most important mechanism, which may be 1,25(OH)₂D₃ dependent. The other mechanism mentioned by DeLuca and Castro is the sodium-calcium exchanger, which according to Castro, functions when the calcium-ATPase is saturated.

Tissues possessing low numbers of vitamin D receptors (VDR) responded to 1,25(OH)₂D₃ poorly when compared with tissues possessing higher numbers of VDR (Goff et.al. 1995). A recent work done by Goff et. al. in 1995 with dairy cows (Jerseys) demonstrated that the variations in a curve of colon VDR concentrations in non lactating pregnant cows were very similar to the ones seen in plasma calcium and 1,25 Dihydroxy vitamin D concentrations during pre-calving,
parturition and first days of lactation (Fig. 7). Although the colon is not a major site of dietary calcium absorption, his work was based in the fact that the VDR in the colon of rats is reflective of the VDR in the duodenum, although colon VDR is generally about 60-70% of duodenal concentration. He also showed in this work, that pre-calving and calving concentrations of VDR in the colon were not significantly different between cows that developed milk fever and those that did not (Fig. 8).

III. Milk Fever Prevention

In ruminants, the absorption of calcium from the intestine is continuous because of the gradual release of food from the fore stomachs. In contrast to monogastrics, ruminants are not prepared for a sudden large demand for calcium as usually happens just after parturition (Westerhuis 1974). Thus, for the cow to adapt to the calcium demands of lactation, calcium absorption and resorption mechanisms have to be rapidly activated at calving to avoid development of hypocalcemia (Goff et. al. 1995).

There are several ways of preventing parturient paresis: reducing calcium:phosphorus ratio in the diet, injection of vitamin D₃ (10 million IU) (Payne 1989), milking pre-partum (Westerhuis 1974), PTH pre-partum administration (Goff et. al. 1986), reducing calcium levels in pre-partum diets, and reducing cation-anion balance in the metabolism. I am going to concentrate in these last two methods, as I believe they are currently the most effective and practical of all.

a. Reducing calcium levels in pre-partum diets

Low calcium diets (<20 gr./d) two weeks prior to parturition will stimulate removal of calcium from bone and calcium absorption in order to maintain normal levels of plasma calcium. Therefore, at parturition, the mobilization of calcium of bone and the active transport of calcium from the intestine will already be activated. Instead, if pre-partum diet is rich in calcium, the input
of calcium into the plasma pool comes mainly from intestinal passive absorption, as the production and activity of PTH and 1,25 dihydroxy D are very low. Thus, at calving, bone calcium resorption induced by PTH and calcium absorption induced by the 1,25 (OH)<sub>2</sub> D<sub>3</sub> will not be readily activated, causing hypocalcemia (Fig. 9).

b. Reducing the difference of cation-anion balance (DCAB)

The concept of balancing rations for anions and cations has been used to optimize the physiological functions of animals. Fixed dietary ion balance is usually calculated as miliequivalents (meq.) of (Na<sup>+</sup> + K<sup>+</sup>) - (Cl<sup>-</sup>). These are called fixed ions, as they are bio available ions that are not metabolized. They are chosen to balance rations for cations and anions, because their importance in ruminant metabolism lies in their indirect participation in osmotic balance, acid-base balance and integrity, and pumping mechanism of cell membranes (Block 1991).

These acidogenic anions (Cl and in some cases also S), are included in the pre-partum diets around 30 days before parturition in the form of salts. The acidifying properties of these salts depend on the preferential absorption of the anion over the cation that makes up the salt. For example, NaCl is a neutral salt, both Na and Cl are efficiently absorbed. CaCl<sub>2</sub>, on the other hand, is an acidifying salt, because Cl is absorbed efficiently (> 90 %), but Ca is absorbed less efficiently (< 40 %). Thus, more equivalents of Cl will be absorbed than Ca. Hence, more H<sup>+</sup> ions will be absorbed to maintain electro neutrality, and the animal will become acidotic (Goff 1991).

It has been demonstrated that the addition of anionic salts in the pre-partum diet can prevent milk fever (Westerhuis 1974, DeLuca 1979, Block 1984 and 1991, Goff 1991 and 1995, Wang 1992, Abu Damir 1994). A recent work by Goff et. al. (1991) suggests that anionic diets may increase activity of preexisting osteoclasts or stimulate proliferation of new osteoclasts. Thus, if more osteoclasts are present in parturition, there will be more osteoclasts available to respond to PTH as lactation begins, speeding the adaptation to the calcium demand (Fig. 10). It is believed
that not only bone calcium resorption is increased by adding anionic salts, but also calcium absorption induced by the 1,25 (OH)\textsubscript{2} D\textsubscript{3} is increased.

c. Acidogenic ions in pre-partum diets and their effects in calcium absorption

Passive and active absorption of intestinal calcium are decreased when high levels of anions are present in the diet. Therefore, even when dietary calcium is high the animal may be perceiving that dietary calcium is low due to low absorption. This will stimulate renal production of 1,25 (OH)\textsubscript{2} D\textsubscript{3} and release of PTH causing bone mobilization prior to parturition (Block 1991).

Chloride moves across the brush border membrane in exchange for bicarbonate (countertransport) in order to maintain electrochemical balance in the lumen (Fig. 11). At the same time hydrogen ions will be obtained from the dissociation of the carbonic acid in the epithelial cell, thus being expelled to the extracellular fluid. Here, calcium will compete with hydrogen ions for binding sites on serum proteins, producing metabolic acidosis. Therefore, urinary calcium and hydrogen excretion will increase, apparently causing formation of 1,25 (OH)\textsubscript{2} D\textsubscript{3} in the kidney, and release of PTH to stimulate bone mobilization.

IV. Conclusions

Cows develop milk fever as a result of the failure of one or both of the hormones (PTH and 1,25 (OH)\textsubscript{2} D\textsubscript{3}) to maintain adequate blood calcium at the onset of lactation. The failure does not seem to be due to inadequate production of the hormones, although there is growing evidence that some cows develop milk fever as a result of delayed production of 1,25 (OH)\textsubscript{2} D\textsubscript{3}. Thus, if production of the hormones is assumed to be adequate, the reason why cows develop milk fever is tissue resistance to the hormones (Goff et. al. 1995). This has been demonstrated by Goff et. al. in
1991, where he proved that bone and renal tissue were refractory to the effects of PTH in the alkaline state, and were stimulated during metabolic acidosis.

The etiology of milk fever is complex, and although in the last decade a lot of facts have been elucidated, there is still a long way to go.