Parturient paresis, or milk fever, is a metabolic disease associated with parturition and the initiation of lactation. It is characterized by low total serum calcium and low or normal serum inorganic phosphorus levels. Outward symptoms are characteristic: In the early stages there may be generalized tetany; in later stages, paralysis and coma. An immediate favorable response usually occurs when the blood calcium level is raised either by the intravenous administration of calcium salts or by the inflation of the udder with air, thus inhibiting milk secretion. The condition occurs most commonly in aged, high-producing Jersey cattle. It is not prevalent at the second lactation and is seldom, if ever, observed in first calf heifers. There are breed differences in susceptibility, Jerseys and Guernseys being more afflicted than Holsteins. High milk production may be a predisposing factor, since reference to this condition first appeared in the literature with the development of high production in the dairy cow.

Before reviewing recent work bearing directly upon parturient paresis, a general survey of the information available concerning some of the aspects of calcium metabolism will be presented to provide a background of information as a basis for discussion of possible methods for the prevention of parturient paresis. The authors are of the opinion that this condition is a failure of the normal homeostatic mechanisms (principally the parathyroid glands) to maintain a normal level of blood calcium in the face of the great loss of calcium from the blood to the milk at the initiation of lactation in the high-producing dairy cow. In order to understand the conditions giving rise to milk fever one must understand these normal physiological mechanisms which become overtaxed.

**Sources, Utilization, and Excretory Routes of Blood Calcium**

The normal blood calcium level of cattle is approximately 10 mg. % (86). The inorganic phosphate of the blood is nearly all completely diffusible between the blood plasma and the extravascular tissue fluids (126). On the other hand, about 30 (126) to 50% (242) of the total serum calcium does not readily pass from the blood. Although there is evidence that a small fraction may be found in the form of a soluble complex of calcium phosphate (168), the great majority of this nondiffusible calcium is bound to serum proteins (13, 149, 157, 242). The diffusible calcium is mostly in ionic form. An equilibrium exists between the ionic and protein-bound fractions of the serum calcium, and the redistribution of calcium between these two states is a rapid process (3, 216). The relationship between ionic calcium and serum protein is relatively constant, making it pos-
sible to estimate the level of the former from the levels of serum protein and total calcium (158).

The level of blood calcium is a reflection of the balance between that which enters and that which leaves the blood. The level is remarkably constant, and rather unphysiological experimental procedures must be undertaken in order to vary the level appreciably. Calcium enters the blood by absorption from the intestine, renal tubular reabsorption, and mobilization from the skeletal reserves. It leaves through the intestine to form metabolic or endogenous fecal calcium, through the urine, by deposition in the bone, and by utilization for growth, pregnancy, and lactation. Each of these sources of supply and loss will be considered in detail in following sections of this review.

The intestinal absorption of calcium. Although the distal portion participates to some extent, particularly when vitamin D is present in the diet (103, 173), calcium apparently is absorbed primarily from the proximal portion of the small intestine, at least in rats. There is evidence that the cæcum and large intestine may absorb some calcium in rats, but this pathway of absorption is far less important than is the small intestine (250).

The calcium content of the diet per se will of course determine the amount of calcium absorbed from the gastro-intestinal tract, and in most species the blood calcium level tends to rise or fall with the dietary calcium level. For example, in sheep (66) and in rats (23, 77, 210, 237), low calcium diets result in a marked decrease in the serum calcium level. In cattle, however, it is difficult to lower the blood calcium level with low calcium diets (82, 159). This may be due in part to the difficulties encountered in attempting to devise low calcium diets for cattle because of the relatively high calcium content of roughages. It has been reported that high calcium diets or those containing a high Ca:P ratio will cause a slight increase of the blood calcium level of cattle (201).

The efficiency of calcium absorption may be increased by two means: (a) increasing the demand of the animal for calcium as during growth or lactation and (b) decreasing the calcium intake. In goats and cattle, the highest level of “true digestibility” of orally administered Ca-45 is reached during the peak of the lactation period (246, 248). Huffman et al. (127) reported a tendency of heavy milking cows to use dietary calcium more efficiently during the period of highest production. Total calcium absorption and retention is increased in rats with low body stores of calcium produced by previously feeding low calcium diets (30, 58, 97, 171). The age of the animal determines the efficiency of calcium absorption. This is probably the result of the greater requirement of the young growing animal for calcium. Calcium absorption decreases with increasing age in rats (30, 94, 111, 112) and in cattle (96). The greater efficiency of calcium absorption in the young animal could be a partial explanation for the low incidence of milk fever in young cattle.

In both rats and cattle, the lower the calcium intake, the greater the efficiency of calcium absorption (94, 127). Animals will adapt to low calcium diets by increasing the efficiency of calcium absorption (175, 176, 249); however, before such adaptation occurs, there must be a substantial loss of the body stores of
calcium (175). Vitamin D may be involved in the mechanism of adaptation, at least in poultry. Chicks will not adapt to low calcium diets with increased intestinal absorption unless vitamin D is present in the diet (163).

Another aspect of the influence of the metabolic requirement for calcium on calcium intake and thus indirectly upon absorption is voluntary self-selection of the diet. Thus, rats on a calcium-deficient diet show a preferential appetite for diets containing calcium (205). Parathyroidectomized rats on a low-calcium diet voluntarily select solutions containing calcium over distilled water (195, 196, 254). Increasing the dietary calcium, administration of vitamin D, or replacement therapy with parathyroid tissue will return the calcium appetite to normal (195, 196).

The formation of relatively insoluble calcium complexes in the intestine tends to limit calcium absorption. Oxalates and phytates are the two most important substances in this respect. Oxalates are known to decrease the absorption of calcium in the rat because of the formation of relatively insoluble calcium oxalate, much of which is excreted as such (226). In adult rats, particularly, the utilization of calcium from calcium oxalate is especially low (146). Oxalates do not play an important role in calcium absorption in ruminants because they are broken down to bicarbonates and carbonates in the rumen. The formation of these compounds may result, however, in alkalosis, thus upsetting mineral equilibrium and affecting calcium metabolism indirectly (226). It has been reported, nonetheless, that oxalates may decrease calcium absorption in ruminants if high levels of potassium are also ingested (225). Phytates, present in rather high levels in cereals, are of considerable importance in calcium metabolism in monogastric animals because they compete for calcium in the intestine and thus limit the amount available for absorption (121, 122, 123, 152, 161, 249). An enzyme, phytase, has been prepared from the intestinal tract of rats (188) and chicks (218). Vitamin D tends to increase the phytase activity of rats and chicks fed with high-cereal rachitogenic diets and those fed noncereal, nonrachitogenic rations (218). Phytates, however, do not appear to be an important factor in calcium absorption in ruminants. In sheep, ingested phytates are completely hydrolyzed in the gastro-intestinal tract, primarily in the rumen (194).

The majority of evidence indicates that an increase in the acidity of the gastro-intestinal tract favors calcium absorption (73, 108). However, the over-all retention of calcium may be unaffected since the oral administration of acid, although it may increase intestinal calcium absorption, also increases the urinary excretion of calcium (72, 108). There is some evidence that increasing the acidity of the gastro-intestinal tract may be beneficial in converting a rachitogenic diet to a nonrachitogenic diet in rats (210).

A few have reported that the Ca:P ratio of the diet is not an important factor in determining the amount of calcium absorbed. Thus, Axelsson and Eriksson (5) found in adult sheep that Ca absorption was directly correlated with the calcium content of the diet and that the amount of dietary P did not influence significantly the absorption of calcium. Patton et al. (187) reported a similar finding in young women, namely, that calcium retention was more
closely dependent upon the absolute level of calcium intake than upon the Ca:P ratio. The majority of evidence, however, indicates that the Ca:P ratio does play a role in determining the absorption of calcium. Thus, in growing calves (180) and in cattle (238) the level of dietary calcium or phosphorus tends to limit the absorption of the remaining element. In rats (26, 210), sheep (57), and goats (83) both the dietary levels of calcium and phosphorus and the Ca:P ratio are important in the production of rickets. There is good evidence that the requirement for vitamin D increases as the Ca:P ratio becomes wider in rats (14). It is assumed that the formation of insoluble calcium phosphate in the digestive tract limits the availability of calcium for absorption. In this connection, Cremer et al. (41) found that vitamin D will increase the absorption of calcium only from insoluble calcium salts, such as calcium phosphate, and has no appreciable effect upon calcium absorption from soluble salts, such as calcium lactate.

Magnesium and manganese, particularly the former, have much the same influence upon calcium absorption as does the dietary Ca:P ratio. Magnesium sulfate supplementation of the diet of cattle decreases calcium absorption, especially if the dietary phosphorus is also low (87, 183). The addition of manganese to the diet of cattle reduces calcium retention (69, 193). In the early stages of magnesium deficiency in dogs there is an increase in calcium retention, presumably due to removal of Ca:Mg antagonism. Thereafter calcium absorption falls, resulting probably from nutritional breakdown (139).

There is some evidence that an increase in the dietary protein will increase the calcium utilization (76, 124), the increase not being entirely accounted for by the increase in growth rate of the rats used in this investigation (76). Although this increase of calcium utilization occurred at both a low calcium and a moderate calcium intake, the protein effect was greater on the latter diet (76). McCance et al. (153) reported similar findings with human subjects. Visek et al. (248) could find no influence of dietary protein on Ca absorption in dairy cattle.

Although Hart et al. (108) could find no consistent or favorable influence of glucose supplementation upon the calcium assimilation of dairy cows receiving a standard ration of alfalfa hay, corn silage, cereal grains, and concentrates, lactose seems to be of some importance in calcium absorption; supplementation of the diet with this sugar increases calcium absorption in calves (198), young boys (164), and lactating rats (64). It has long been known that diets rich in lactose tend to prevent tetany and prolong the lives of parathyroidectomized dogs (45, 46). This is true only if the diet contains, in addition to lactose, relatively high levels of calcium (81).

Moderate amounts of dietary fat apparently favor (25, 132), and larger amounts depress, calcium absorption (67) probably because of the formation of insoluble calcium soaps. It has been proposed that the favorable influence of fat is due to the formation of a readily absorbable bile-fattyacid-Ca complex (67). The action of fat upon calcium absorption also seems to depend upon the calcium and phosphorus content of the ration, since supplemental fat is more effective in increasing the utilization of calcium from diets containing optimum amounts of phosphorus as compared to low P diets (27, 132). In rats, the utiliza-
tion of calcium from calcium soaps may be dependent upon the demand for calcium and upon the presence of vitamin D (172). It has been reported that the degree of saturation of the soap is (12), and is not (172), important with regard to the absorption of calcium from soaps. In adult humans, the fat content of the ration appeared to have little or no influence upon the absorption of calcium (68, 219).

Vitamin D, with the exception of the dietary calcium intake, is the most important factor in regulating the absorption of calcium (174). Experiments in the early 1920’s (107, 156) indicated that a dietary factor present in green feeds and cod liver oil, which was distinct from the antiscorbutic factor and fat-soluble A, would increase calcium retention in rats and goats. Exposure of dry and lactating goats (105) or lactating cows (106) to artificial ultraviolet light or sunlight would also increase calcium retention. It is now generally accepted that vitamin D has a direct effect upon the mineralization of bone, as well as upon the intestinal absorption of calcium (75). The influence of this vitamin on bone will be considered in another section of this review. Most evidence indicates that the action of vitamin D upon the intestine is confined to a direct effect upon calcium absorption, the decrease in the absorption of phosphorus observed in vitamin D deficiency being due to the precipitation of P by the increased levels of unabsorbed calcium (170). There is evidence that vitamin D increases intestinal calcium absorption only under conditions in which the intestinal calcium is poorly soluble (41, 103). Bile is required for the action of vitamin D (74, 116). It has been proposed on the basis of studies with poultry that the action of vitamin D may be explained by its reaction with calcium at the intestinal absorptive barrier. Thus, the amount of calcium absorbed in the presence of excess vitamin D would be a function of the amount of vitamin D–calcium complex formed (163).

**Endogenous or metabolic fecal calcium.** In rats (250) and cattle (95) the use of parenterally administered Ca-45 has indicated that calcium is excreted into the feces through all parts of the gastro-intestinal tract, but the small intestine is by far the most important excretory pathway. In cattle, the amount of endogenous fecal calcium is directly proportional to body weight and is little influenced by short-term dietary changes (38, 247). After correcting for increase in body size, there is some indication that endogenous excretion increases slightly with age (96). When cattle are fed low-calcium diets for prolonged periods, there is a decrease in the excretion of endogenous fecal calcium (38). There is evidence that the amount of endogenous fecal calcium is influenced by vitamin D. Thus, in rats on a calcium- and phosphorus-free diet, vitamin D lack increased the excretion of metabolic fecal calcium (169). The amount of unabsorbable calcium in the intestine may also determine the extent of metabolic calcium excretion. Thus, ingestion of high oxalate diets and the administration of chelates or calcium phosphate to rabbits increased the excretion of metabolic fecal calcium (232). The supposition is that an unabsorbable calcium reservoir in the intestine competes for blood calcium across the intestinal wall.
Urinary excretion of calcium. In normal dogs over 99% of the calcium filtered through the glomeruli of the kidney is reabsorbed by the renal tubules (168). In rats 90-97% is reabsorbed (39). It appears that the renal clearance of calcium is dependent upon the ability of the renal tubules to reabsorb ionic calcium and upon the concentration of ionic calcium in the serum (168). In general, the extent of calcium excretion in the urine depends upon endogenous (hormonal) factors which regulate tubular reabsorption and the serum calcium level and upon the dietary calcium intake per unit body weight (136, 175). Sex, age, and dietary factors other than calcium, with the exception of ingested acids, have only minor effects upon urinary calcium excretion (136). Ingestion of mineral acids by human subjects (136) and cattle (108) increases urinary calcium excretion.

Utilization of calcium for growth, pregnancy and lactation. Pregnancy and particularly lactation tend to lower the level of blood calcium as a result of the transfer of blood calcium to the fetal skeleton and to the milk. For example, Niedermeier et al. (177) have demonstrated a greater, more consistent decline in the serum calcium level of intact cows at parturition (initiation of lactation) than in mastectomized cows. Under normal conditions, however, blood calcium does not fall appreciably with pregnancy and lactation (244) except for a transient fall of the level of blood calcium with the initiation of lactation (15, 71, 151, 177). This is true even though lactating cows are in negative calcium balance during at least the first part of the lactation period (63, 251). The fall occurs in both the diffusible fraction and in total blood calcium (151). However, if another calcium stress, such as low calcium diets or parathyroidectomy, is imposed upon the stress of pregnancy or lactation, there may be a marked fall in blood calcium (24, 66) and an increase in maternal and fetal mortality (21). This is not always the situation. Duckworth and Hill (47) fed low-calcium diets to ewes throughout pregnancy and lactation with no reduction of reproductive performance, milk production, or lamb survival. Although pregnancy does not induce marked mobilization of skeletal calcium reserves (24, 253) lactation does (65), particularly on low calcium diets (24, 47).

Equilibrium between calcium of the blood and bone. Calcium transfers readily between the blood and the bone, the direction of transfer depending upon the current demand of the soft tissues for calcium. A large amount of calcium can be removed from the blood within a short time without resulting in an appreciable fall of the level of blood calcium because of the rapid mobilization of skeletal calcium (109, 110). Actually, bone resorption and deposition occur in all bone constantly, although both processes are more rapid in regions of active growth. Decalcification occurs when the rate of resorption exceeds the rate of deposition (131). The skeleton is a calcium reserve which releases calcium to the blood when it is needed and stores it avidly when the availability of calcium from intestinal absorption exceeds the requirements of the soft tissues (10). Thus, in rats and cattle approximately 85% of an intravenous dose of Ca-45 or of the Ca-45 absorbed from the intestine is deposited in the bone (93).
The skeletal calcium consists of two components on the basis of the rate of exchange between the calcium of the blood and that of the bone (212, 213, 215). One fraction, the "labile" fraction, exchanges rapidly with blood calcium and is believed to consist of calcium located on the surface of the microcrystals of the bone salt (69, 215). It has been reported that not all of the crystal surfaces are involved in this rapid exchange. Engfeldt and coworkers (52, 54) have demonstrated that only the young Haversian systems have a high rate of uptake, the older systems picking up the isotope slowly. It may be that the young areas take up isotope more readily because of the smaller size of the bone crystals in the newly formed areas (54). The other component of the bone calcium, the "stable" component, exchanges slowly with blood calcium and may consist of calcium within the interior of the bone crystal where exchange occurs by the recrystallization of bone salt (215). It has been reported that the crystallization and recrystallization processes which remove calcium from the exchangeable, that is labile, component to the stable component of the bone calcium occurs at a rapid rate. Thus, one hour after the administration of Ca-45 into rabbits one-half of the isotope fixed in the bone is no longer exchangeable by the usual in vitro techniques (1). This may account, at least in part, for the failure of Carlsson (31) to find a "labile" fraction in the rat incisor.

The size of the labile component varies with age, the size being greater in the young animal (40, 102). In fact, nearly all of the skeletal calcium of young rats exchanges rapidly with that of the blood (102). If this situation is true in cattle, this may be another reason for the increase in the incidence of parturient paresis with age in cattle. Estimations of the size of the labile component in older animals vary from 15 to 33% of the total skeletal calcium (40, 43, 59, 120, 235). There is good evidence that different bones have different rates of exchange, depending upon their anatomical location (219). In fact, different areas of the same bone have different rates of exchange. Thus, in rats epiphyseal bone exchanges more rapidly than does diaphyseal bone (2, 101, 102).

**FACTORS REGULATING THE LEVEL OF BLOOD CALCIUM**

Although some of the information available relating to the sources of calcium supply and loss and the pathways of calcium metabolism has been reviewed, little mention has been made of the regulators which act to maintain a constant level of blood calcium in the face of wide fluctuations in calcium supply and demand.

**Influence of vitamins upon calcium metabolism.** Although vitamin A is reported to have an influence upon bone metabolism (8, 129), possibly regulating the gross shape and structure of bone (160), vitamin D is by far the most important nutritional factor in regulating calcium metabolism, with the exception of calcium itself. As mentioned above, vitamin D has two effects upon calcium metabolism. It regulates intestinal absorption and it has a direct influence upon the bone. Thus, it apparently is involved in regulating the pathway between skeletal calcium and blood calcium. It is this latter function with which we are concerned in the present discussion.
A large number of investigators have demonstrated that vitamin D will cause bone resorption. Barnicot (8) found that crystals of vitamin D, but not cholesterol, will cause local resorption of bone when grafted to bone. In rats fed low-calcium diets vitamin D will induce bone resorption (99). Vitamin D administration will induce hypercalcemia in dogs (114, 133) and rats (208, 227) fed low Ca or calcium-free diets to minimize the influence of the vitamin upon intestinal calcium absorption. Massive doses of vitamin D will also cause increased blood calcium levels in cattle (48, 115, 118, 141). In this case, increased intestinal absorption of calcium as well as mobilization from the bones could account for the increase in blood calcium.

Vitamin D will protect parathyroidectomized animals against tetany by tending to maintain the blood calcium at normal levels even when such animals receive a calcium-free diet (133). This vitamin, especially dihydrotachysterol, has been used successfully in the treatment of parathyroid insufficiency in humans (200). Dihydrotachysterol is effective in this respect even when such patients are receiving a low-calcium diet (199). It will increase the blood calcium level to a much greater extent than would be predicted by its anti-rachitic properties (155). Actually, any of the compounds having vitamin D activity are more effective in the treatment of parathyroid insufficiency than is parathyroid extract itself (154). Parathyroidectomized dogs receiving vitamin D in amounts sufficient to maintain normal levels of blood calcium and phosphorus can complete a normal life cycle, including reproduction and lactation (137).

Carlsson (32) observed that vitamin D increased the Ca-45 uptake by bone but did not increase the bone ash weight of rats on a low calcium diet. This type of diet was used in order to minimize the influence of the vitamin upon intestinal calcium absorption. From these results it was concluded that vitamin D favors bone resorption. This conclusion was further substantiated by the fact that the blood calcium level remained normal in spite of the low calcium diet in the vitamin D-treated animals. It appears that the hypocalcemia in vitamin D-deficient rats may be due to an inability to utilize stored bone salt even when such stores are filled by previous diets adequate in calcium and phosphorus. In such vitamin D-deficient rats, the blood calcium falls within 24 hours after the rats are placed on a low calcium diet (33). Singer and Armstrong (214) reported that vitamin D does not alter the turnover rate of the “stable” fraction of bone calcium. It would appear that vitamin D functions primarily in intestinal absorption but that it also is involved in maintaining a normal blood calcium level by skeletal mobilization of calcium when calcium availability is limited.

Influence of hormones upon calcium metabolism. There is evidence that the administration of thyroid hormone will increase the excretion of fecal calcium in intact and hypophysectomized rats (192), in dogs (113), and lactating dairy cattle (181). There is no effect upon the serum calcium or phosphorus levels of cattle (181), dogs (143, 150), or guinea pigs (178). Engfeldt and Hjertquist (53, 55), however, have reported that thyroxin and pituitary thyrotrophic hormone, in the presence of an intact thyroid, will increase serum phosphorus and decrease the serum calcium, thus resulting indirectly in parathyroid stimulation.
in the rat. Thyroxin has little or no influence upon urinary calcium excretion (181, 192) and any increase which may occur is due to general diuresis with no change in the concentration of urinary calcium (150). There is good indication that prolonged administration of thyroid hormone (178) or excess endogenous production of thyroid hormone (62, 178) may result in excessive bone destruction.

Cortisone administration to growing rats decreases the normal osteolytic activity at the ends of the long bones to such an extent that a dense zone of calcified cartilage matrix is formed (60). This is unique with the rat and does not occur in mice, guinea pigs, or rabbits (61). It has been reported that cortisone administration to nephrectomized dogs increases serum calcium to high levels along with a rise in serum magnesium and phosphorus (84). Ulrich et al. (241) reported that the prolonged injection of ACTH causes a slight increase in urinary and fecal Ca-45 excretion in both hypophysectomized and intact rats but has little effect on the skeletal uptake. Hypophysectomy alone decreased the skeletal uptake of Ca-45.

Krishnan (138) reported that daily injection of “Antuitrin” growth hormone preparation increased calcium retention and decreased fecal calcium excretion but had no effect upon urinary calcium excretion in guinea pigs and rats. Ulrich et al. (240) found that “pure” growth hormone increased the tibial uptake of Ca-45 in hypophysectomized rats as compared to hypophysectomized controls but no change in calcium content of bone ash occurred. In acromegaly there was an increase in the urinary calcium and phosphorus excretion, although the blood levels remained normal (9). Engfeldt (51) reported that the administration of growth hormone to hypophysectomized rats increased the blood phosphorus level, thus stimulating the parathyroid activity indirectly. Administration of growth hormone to hypophysectomized-parathyroidectomized rats also increases blood phosphorus; thus, the increase in blood phosphorus was not due to the parathyroid hormone. Hertz and Kranes (113) reported that parathyroid hypertrophy and hyperplasia occurred in rabbits with the injection of anterior pituitary extract. Törnblom (236) found that the pituitary has no direct influence upon the parathyroids but does increase blood phosphorus and tends to decrease blood calcium. It is suggested that the increase in blood phosphorus is the stimulus to the parathyroids. Some evidence is presented indicating both growth hormone and ACTH are responsible for the increase in blood phosphorus, probably by way of their influence upon carbohydrate metabolism.

The influence of estrogen on calcium metabolism in birds has recently been reviewed by Lorenz (144). Although estrogens have no influence on the level of blood calcium in mammals (140), they have an effect upon the skeletal system, the nature of the influence depending upon the species. Urist et al. (243) have found that estrogens stimulate endosteal bone formation and inhibit bone resorption in mice. In the young growing rat endosteal bone is not produced but endochondral bone formation is interfered with because of the inhibition of the normal resorptive processes involving the cartilage matrix and new bone. Estrogens have no specific effect on guinea pigs, rabbits, cats, or dogs although proliferation of the epiphyseal cartilage and new bone formation may be depressed.
Vitamin D does not play a role in the mechanism of estrogen-induced endosteal bone formation in mice (206).

The hormone secreted by the parathyroid glands is one of the most important factors regulating the level of blood calcium. Salvensen (202) concluded that the symptoms of parathyroid removal were due to calcium deficiency and that the parathyroids normally regulate the level of blood calcium on the basis of observations that parathyroidectomized dogs would survive if fed high calcium diets and that the intravenous administration of calcium salts would cure and prevent the tetany resulting from this operation. In a series of experiments, Collip (37) demonstrated that extracts of the parathyroids would increase the blood calcium level of intact and parathyroidectomized dogs. Greenwald and Gross (80) found that similar extracts resulted in the excessive destruction of bone, increased the serum calcium level, and increased urinary phosphate excretion. Hastings and Huggins (110) repeatedly removed, decalcified, and transfused the decalcified blood into dogs and found that under such conditions the blood calcium level was maintained more readily in intact than in parathyroidectomized dogs. From these results it appears that although skeletal mobilization of calcium can occur to some extent in the absence of the parathyroids, parathyroid hormone is important for such mobilization. Observations by Bodansky and Duff (22) have also suggested an inability of the parathyroidectomized animal to mobilize skeletal calcium. They observed a failure of the pregnant, parathyroidectomized rat to maintain a normal serum calcium level. At the conclusion of pregnancy the long bones of the parathyroidectomized animals weighed more, in relation to the pregestational body weight, than those of the intact controls. The per cent ash of the bone was also higher in the former group, whereas the calcium/phosphorus ratios were nearly identical. Parathyroid hormone has no influence upon the intestinal absorption of calcium (220).

It has been known from the early work of Greenwald (78) and Greenwald and Gross (79) that parathyroid removal results in marked phosphate retention by the kidney. These early findings have been confirmed and extended by the work of Talmage and Kraintz (228, 229), who have demonstrated an immediate decrease in urinary phosphate excretion after parathyroidectomy in the rat. The administration of parathyroid extract results in an increase in phosphate excretion. This increase is due, at least in part, to a decrease in the renal tubular reabsorption of phosphate (29, 100, 104, 135). An increase in the glomerular filtration rate may (135) or may not (29) be partially responsible for the increase in urinary phosphate excretion. These differing results may be due to the particular extract employed. Both the nature of the extract and the route of administration are important to the manner in which parathyroid extracts cause increased urinary phosphate excretion. Handler and coworkers (90, 91, 92) have observed that the intravenous administration of parathyroid extract will increase the urinary phosphate excretion of dogs. This increase is associated with increased renal blood flow and glomerular filtration rate, which are secondary to an increase in systemic blood pressure. The subcutaneous administration of similar extracts, on the other hand, increases phosphate excretion by
reducing the tubular reabsorption of phosphate without changing the glomerular filtration rate. In the latter instance the serum calcium increased to high levels. Chemical fractionation of the extract produced two components: one which would increase glomerular filtration rate, the other which increased the blood calcium level and reduced tubular phosphate reabsorption. Stewart and Bowen (222) have confirmed previous findings that the intravenous administration of parathyroid extract will induce an immediate increase in renal phosphate excretion. They believe this to be an artifact since similar activity could be demonstrated in extracts inactivated, as regards their ability to raise serum calcium, by formaldehyde treatment. Further, similar activity could be demonstrated in extracts of spleen and kidney prepared in the same manner as parathyroid extract. Davies and Gordon (42) have also prepared a fraction from parathyroid extract that will increase phosphate excretion without increasing the serum calcium level. Since glomerular filtration rates were not measured in these last two studies, it cannot be determined if the factor causing increased urinary phosphate excretion is similar to that prepared by Handler and coworkers. The extract of the latter increases the glomerular filtration rate without increasing tubular reabsorption.

The early work with the parathyroids led to two conflicting opinions regarding the actual mechanism by which these glands increase the level of blood calcium. One school of thought (1) supported the view that "... the parathyroid hormone in some way affects the phosphate dissolved in body fluids in such a way as to make it more readily excreted by the kidney with a resulting decrease in the serum phosphorus values; resorption of the calcium-phosphate salt from the bone-resorbing surfaces is thereby increased; there results an elevated serum calcium level together with the depressed serum phosphorus level. Once this new state of equilibrium has been reached there would be no further changes if it were not for the fact that the higher serum calcium level leads to an increased calcium excretion in the urine; this loss of calcium in the urine is a factor tending to cause undersaturation of the body fluids again so that unless there is a supply of calcium from the gastro-intestinal tract the bones will have to supply the deficit." Thus, the primary action of parathyroid hormone, in the opinion of this group, is an increase in the renal excretion of phosphorus, the other changes such as the increase in blood calcium being secondary effects. The other school (233) proposed that the primary action of the hormone was to induce dissolution of bone, possibly by increasing the numbers and activity of the osteoclasts of bone.

At the present time there is good evidence that endogenously produced parathyroid hormone and certainly parathyroid extracts have direct effects on both the renal excretory mechanisms and the bone. It is known that the increase of phosphate excretion, which occurs with parathyroid extract administration, precedes the rise of blood calcium (1). As mentioned above, such extracts result in an active decrease in the tubular reabsorption of phosphate. Schaal and Kyle (204) have demonstrated that in human hyperparathyroidism with attendant hypercalcemia the renal tubular phosphate reabsorption is low. If a similar
hypercalcemia is induced in normal controls by the intravenous administration of calcium salts, however, phosphate reabsorption does not change unless parathyroid extract is also administered, in which case it decreases. Thus, something is present in the hyperparathyroid which actively reduces phosphate reabsorption irrespective of hypercalcemia. Milne (165) has reported a low urinary phosphate clearance in a hypoparathyroid patient which returned to normal upon parathyroid extract administration. Similar injection into normal people had no effect upon phosphate clearance, and it was suggested that the primary action of the extract in the hypoparathyroid individual is a renal one, whereas under normal conditions the hormone stimulates osteoclastic bone resorption.

Talmage and Kraintz (228) have found that the renal excretion of injected P32 is greatly reduced within one hour after parathyroidectomy in rats. In an extension of these studies, Talmage and Kraintz (229) reported an immediate increase in the renal Ca-45 excretion along with the reduced phosphate excretion. The excretory rates returned to normal within 24 hours in spite of the continued high blood phosphorus and low blood calcium levels. The same picture in reverse occurred in normal rats injected with parathyroid extract, except that the excretory rate of phosphate remained above normal. From these results the authors concluded that the parathyroids have a direct effect on the renal excretion of both calcium and phosphorus. The return of the excretory rates of calcium to normal is explained as a change in the renal threshold for calcium. When serum calcium becomes adjusted to the new level, calcium excretion returns to normal. Excretory changes observed after the adjustment of the serum calcium and phosphorus levels to new thresholds are due to extra-renal changes which increase or decrease the entry of calcium and phosphorus into the serum. In an earlier paper, Talmage and coworkers (231) reported that parathyroid extracts remove significant amounts of previously deposited Ca-45 and P32 from the subepiphysseal plate region of the long bones of rats. The amount of phosphorus removed appeared greater than the amount of calcium removed. They assumed that the parathyroids act directly upon the bone but that this effect is enhanced by the additional effect upon the kidney, where phosphate excretion is increased since the serum P levels can be increased above normal by extending hormone treatment in spite of the greatly elevated renal phosphate excretion, indicating mobilization of skeletal phosphate.

It has been definitely established that the parathyroids can have a direct influence upon bone resorption. Barnicot (7) and Chang (36) have found that local grafts of parathyroid tissues to bone result in local bone resorption, whereas similar grafts of other tissues, such as thyroid or adrenal, do not. Although early work indicated that the administration of parathyroid extract to nephrectomized animals would not result in increased serum calcium levels (167, 239), later reports have demonstrated that this response will occur in the nephrectomized animal (134, 221, 223, 230) and that this response could still be elicited several weeks after nephrectomy when the animal is maintained by intraperitoneal lavage (85). Nephrectomy alone will result in parathyroid stimulation and induce bone changes similar to those produced by the administration of parathyroid
extract (128, 207). Parathyroid extracts produce the bone lesions typical of hyperparathyroidism in nephrectomized, as well as intact, rats (128). Jacobs (130) has found that preventing the drop of blood phosphorus, which usually occurs with parathyroid extract administration, by the intravenous administration of phosphate will still result in an increase of the blood calcium, indicating that extra-renal mechanisms regulate the serum calcium level in this case. Monahan and Freeman (166) came to a similar conclusion upon finding that the serum calcium level decreased 50% within 72 hours in nephrectomized, parathyroidectomized dogs but no similar decrease occurred with nephrectomy alone. In a different approach to the problem, Stewart and Bowen (221) found that the intravenous administration of oxalate lowered the serum calcium level to about 6 mg. %, the level returning to normal within 6 hours in intact, as well as nephrectomized, dogs. In parathyroidectomized dogs a similar decrease in this "oxalate tolerance" curve occurred but there was no return to normal within 6 hours, indicating that the parathyroids regulate blood calcium independently of the kidney. Recent evidence indicates that the parathyroids may destroy the organic matrix of bone, thus liberating bone salt indirectly. Carnes (31) found that bone matrix may be broken down by parathyroid extract irrespective of its mineral content. The resulting level of serum calcium and the severity of metastatic calcification that occurred were functions of the mineral content of the resorbed matrix. Engel (49) and Engel et al. (50) reported that parathyroid extract causes depolymerization and solution of the glyco-protein ground substance of bone and epiphyseal cartilage. There was an associated increase in the serum mucoprotein level, which was related to the degree of bone change and roughly to the amount of hormone administered. It was suggested that the effect of parathyroid extract is brought about by its influence on the state of the mucoprotein of bone and cartilage.

From results reported in the literature it is difficult to assess the importance of the parathyroids in calcium metabolism of ruminants. Parathyroidectomy appears to cause a decrease in the serum calcium level of goats (28). Robinson et al. (197) reported that the administration of rather high levels of parathyroid extract to calves resulted in a great increase in the serum calcium level. Hibbs et al. (119) found only a small increase of the blood calcium level of cows that received a single subcutaneous injection of 2,000 to 3,000 units of parathyroid extract. Lotz et al. (145) reported that the administration of 1,000 to 3,000 units of parathyroid extract to sheep resulted in the removal of previously deposited P32, but not of Ca-45, from the skeleton. The blood phosphorus level increased; the blood calcium level remained normal. There was a slight increase in the urinary phosphate excretion, which could be accounted for by the increase in the level of blood phosphorus. They concluded that in sheep the parathyroid extract acts directly upon bone to remove primarily phosphorus.

The primary stimulus to parathyroid secretion is the level of the serum calcium (56, 185, 186), and factors that result in hypocalcemia will stimulate the parathyroids whereas those resulting in an increased blood calcium level will depress parathyroid activity. Pregnancy had been shown to result in increased
parathyroid size in rats \((179, 211)\), especially when superimposed on low calcium diets \((211)\). Pregnancy may not affect parathyroid size in rabbits and goats but lactation does \((28)\). Growth hormone \((51, 236)\), ACTH \((236)\), thyrotrophic hormone and thyroxine \((53, 55)\) and anterior pituitary extracts \((17, 113)\) increase parathyroid activity. Nephrectomy, as well as urethral ligation will increase parathyroid activity \((6, 179, 190)\) as will renal disease in humans \((184)\). The intravenous injection of calcium salt into dogs and rabbits will cause parathyroid depression; the administration of phosphate causes hyperplasia \((189)\). In fact, if the ingestion of high levels of phosphate salts is continued for prolonged periods, bone changes characteristic of hyperparathyroidism may occur \((203)\). Low-calcium diets increase parathyroid activity whereas high-calcium diets decrease the size and activity of these glands in rats \((28, 35, 44, 56, 89, 98, 147, 203, 211, 224, 234)\), rabbits \((11)\), birds \((148)\), swine \((142)\), and sheep \((18)\).

**Milk Fever**

*Review of literature.* In view of the excellent review of parturient paresis in dairy cattle by Hibbs \((117)\) a detailed survey of the literature in this field is not warranted. Some of the pertinent information published subsequent to this review will be discussed.

A number of reports have appeared indicating an apparent association of adrenal cortical activity with milk fever. A decrease of serum citric acid \((16, 252)\) and higher serum pyruvic and lactic acid levels \((252)\) have been reported in cows exhibiting symptoms of milk fever in comparison with normally calving controls. It has been suggested that a failure of the glycolytic cycle occurs in milk fever \((252)\). Van Soest and Blosser \((245)\) found a marked increase of blood glucose and pyruvic acid in both normally calving cows and in cows developing milk fever, the levels being considerably higher in the latter group. Statistically significant negative correlations between blood glucose and plasma phosphate and between blood pyruvate and phosphate were observed in the cows with milk fever. The correlation between blood glucose and pyruvate was positive and highly significant in both normally calving and milk fever cows at parturition. The authors suggest that these changes may be associated with an increased output of adrenal hormones. In this connection, Garm \((70)\) has reported marked lymphopenia and eosinopenia as well as adrenal cortical hypertrophy in cows with milk fever and has suggested this condition is a "disease of adaptation" \((Selye)\). Holcombe \((125)\) has found that cows with milk fever show a low excretory level of urinary-reducing corticoids and neutral steroids, indicating adrenal cortical exhaustion. Since a decrease in the circulating lymphocytes and eosinophils and an increase in neutrophils and blood sugar occurs at parturition, Merrill and Smith \((162)\) suggest that an increased secretion of adrenal cortical hormones occurs in response to the stress of parturition. The administration of ACTH has a similar effect to that of parturition on these blood constituents. In a continuation of this study \((217)\) these workers report that milk fever produces sufficient stress to increase adrenal cortical activity as measured by the leucocyte response. In such cows adrenal cortical exhaustion was not evident since ACTH
administration resulted in the usual typical response. It would appear that the change of adrenal cortical activity associated with milk fever is not the cause but rather the effect of the stress imposed by this condition.

Ward et al. (251) have determined mineral balances in dairy cattle before and after parturition. They observed a severe negative calcium balance for about 15 days prepartum in three mature Jersey cattle that developed milk fever after parturition. The prepartal calcium balances were positive in mature Jerseys that did not develop milk fever and in first calf heifers. In all three groups calcium balances were negative after parturition. The authors suggest that milk fever may be preceded by a period of defective calcium absorption from the intestine or by excessive excretion of endogenous fecal calcium.

Owen (182) has studied the influence of complete milking at calving time on the incidence of milk fever. Ayrshire, Guernsey, and Jersey cows were divided into three groups at parturition. One group was partially milked for 3 days after calving. The second group was completely milked by conventional methods; in a third group the completeness of milking was aided by the administration of oxytocin 2 hours after calving. From the results, it was suggested that complete milking had no appreciable influence on the occurrence of milk fever. The incidence of this condition was so low in all three groups, however, that it is difficult to arrive at a definite conclusion in this respect.

In an interesting survey of parturient paresis, Hallgren (88) has studied 881 cases of "milk fever" in Sweden. Approximately 85% of the animals classified by field diagnosis as exhibiting symptoms of milk fever responded immediately to intravenous calcium therapy. Blood samples were collected from 77 of the animals that did not immediately respond and were analyzed for serum calcium, magnesium, phosphorus, and potassium. Only 12 of these cases were "normal" milk fever characterized by low serum calcium level. A second course of calcium therapy was effective in relieving the condition. Nine of the cases were "down" as a result of a severe primary heart condition; hypocalcemia was not manifest. A large number of the remaining animals were classified as "downers." In this condition the animal is alert but unable to rise. The serum calcium level may be low or normal and the serum phosphate level is low, often virtually nonexistent. Such animals respond favorably to intravenous phosphate administration. This report emphasizes the fact that a number of disorders may occur in high-producing cows coincident with parturition, which are often indistinguishable from "true" milk fever without a determination of the levels of serum calcium and phosphorus.

Prevention. The majority of evidence accumulated through the years concerning the etiology of parturient paresis strongly indicates that this condition results from a failure of homeostatic factors (principally the parathyroid glands) that normally operate to maintain the blood calcium at a constant level in the face of the drain of calcium to the milk with the initiation of lactation. On this basis the approach to milk fever prevention would involve either the preparation of these physiological mechanisms for optimal activity in advance of the demands of lactation or the temporary substitution of these mechanisms by artificial means.
until they can become sufficiently active to meet the requirements of lactation
by the adequate mobilization of calcium. Calcium lost from the blood can be re-
placed in only two ways, either by increasing the intestinal absorption of calcium
or by increasing the mobilization of previously deposited skeletal calcium. At-
ttempts to prevent milk fever by increasing the calcium content of the diet have
been ineffective. This is probably because the extent of intestinal absorption
cannot meet the lactation requirement of the high-producing cow, particularly
after a period of low calcium demand (last portion of preceding lactation and
the dry period) and in older animals when the efficiency of calcium absorption
may be reduced. Thus, the better approach to milk fever prevention seems to
be the stimulation of the mobilization of bone salt either by activating the normal
endogenous factor (parathyroids) before lactation begins or by causing the
mobilization of bone salt by artificial methods until the former mechanism can
assert itself. The two methods of prevention, one proposed by Hibbs and Pounden
(118), the other by Boda and Cole (20), which hold the most promise to date
are based on these premises.

Hibbs and Pounden (118) have presented a summary of their work of the
past several years on the influence of the prepartal oral administration of massive
doses of vitamin D₂ (30 million units/day) on the incidence of milk fever. Their
results indicate that milk fever can be largely prevented by this procedure. In
cows receiving such treatment the usual fall of serum calcium and phosphorus
at parturition is prevented, probably as a result of the skeletal mobilization of
bone salt. Some increase in the intestinal absorption of these elements may also
occur. These workers are of the opinion that the effect of the vitamin is to replace
the calcium mobilizing effect of endogenous parathyroid hormone during the
critical period at parturition. Previous attempts to reduce the incidence of milk
fever by feeding smaller doses (1 to 5 million units of vitamin D₁ per day) for
prolonged periods (2 to 4 weeks) were unsuccessful. This was attributed to an
insufficient calcemic effect at parturition coupled with inhibition of parathyroid
activity resulting from the prolonged prepartal elevation of the blood calcium
level. The major disadvantage of this method is that the expected calving date
must be rather accurately predicted so that the vitamin may be administered
for at least 4 or 5 days but no longer than 7 days before parturition because of
the possibility of hypervitaminosis with associated calcification of the soft tissues.
Although these workers have used vitamin D₂ in their studies, it would be inter-
esting to determine the dose of dihydrotachysterol required to prevent milk fever
in view of its much more pronounced calcemic effect than either vitamins D₁ or
D₂.

The second approach to milk fever prevention is that suggested by Boda and
Cole (19, 20), which is based upon the use of low-calcium, high-phosphorus pre-
partal diets in order to stimulate the production of endogenous parathyroid hor-
mone by causing stimulation of these glands before the initiation of lactation
and the increased demand for calcium mobilization occur. The evidence indicates
that this procedure is effective in reducing the incidence of milk fever in high-
producing Jersey cattle. The low-calcium prepartal diets are not detrimental
to milk production, parturition, or the health of the calf. This aspect has been discussed in detail by Boda in a recent paper (19). The major disadvantage of this procedure is one of management imposed by the apparent necessity of feeding extremely low calcium rations. This requires a rather marked restriction of the intake of roughages, which are relatively high in calcium. Thus, the dry cows must be maintained in a dry lot and fed individually for the last month of the dry period in order to reduce the calcium intake and minimize the possibility of bloat, which might occur by group feeding these preventive rations which contain a relatively high proportion of concentrates to roughage. The rations that have been used to date have consisted of oat hay and either ground barley supplemented with mono-sodium phosphate (technical grade) or a basic concentrate mixture consisting of barley, wheat bran, cottonseed meal, and the phosphate salt. Daily intakes of hay varied from 5 to 8 lb.; concentrates from 8 to 12 lb. for a 1,000-lb. animal. It may be that the modification of the diets now in use for milk fever prevention, such as the addition of low-calcium grass silage or the incorporation of scabrous and bulky material to the ration, will minimize the basic management problem.

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