Common Metabolic Diseases of Cattle: Ketosis, Milk Fever, Grass Tetany, and Downer Cow Complex[1]

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INTRODUCTION

Reid, in the 50th anniversary issue of the *Journal of Dairy Science*, stated that "in 1906, the average cow in the United States produced approximately 2,500 lb of milk; in 1956, she produced more than 5,000 lb." During the next 25 yr, the average annual milk production per cow has more than doubled, and some individual herds average more than 9,000 kg per cow per year. Selection of vastly improved strains of cattle in addition to increasing the potential for milk production also drastically narrows the nutritional and management spectrum over which these animals can maintain metabolite homeostasis. Thus, proper nutrition and management of these high-producing cows become increasingly complex and critical.

This review is not a comprehensive review of major metabolic diseases of cattle; rather, it is intended to be an interpretative summary. Emphasis will be placed upon progress during the last 25 yr, upon new techniques and approaches that have enhanced our understandings, and especially upon future areas in which research could be profitable or is needed strongly. We have reviewed major achievements as we see them in understanding pathogenesis of lactation ketosis, milk fever, grass tetany, and downer cow complex, and we have speculated upon future areas of research that seem worthy of additional investigation for these diseases. References will be limited to general reviews when possible, with emphasis on the most current reviews.

LACTATION KETOSIS

Ketosis, or acetonemia, is an increase of "ketone bodies" (acetone, acetoacetate, and β-hydroxybutyrate, subsequently referred to as ketones) in blood until they eventually begin to spill over into urine and (or) milk. In dairy cows, ketosis is a lactation disorder usually associated with intense milk production and negative energy balance.

Importance

Ketosis can be either clinical or subclinical; therefore, the incidence of ketosis and resulting financial losses are difficult to quantitate. Lactation ketosis is a worldwide problem in cows producing greatest amounts of milk. The average incidence has been about 4% in the United States and 2% in the United Kingdom (94, 96). Incidence is not influenced by breed (98), but cases seem to increase in winter (94). Individual herds can have widely differing incidences (98) that may be 40% or greater. Hibbitt (39) reported that in some herds in the United Kingdom, up to 33% of cows tested positive for milk or urine ketones, lost weight, and had decreased milk production. Emery et al. (26) reported that about 50% of the cows in some high-producing herds had at least subclinical ketosis and that 20 to 30% of the subclinical cases developed into clinical ketosis. Death from lactation ketosis is not common.

With clinical ketosis, need for treatment and losses of milk production are obvious whereas with subclinical ketosis, neither is obvious, and the cow just "does not do well." Financial

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losses are from decreased milk, decreased body weight, cost of treatment, disposal of cows that have recurring cases, and possibly death. If 500,000 cows are treated annually in the United States and if milk is reduced 454 kg per cow during the remainder of that lactation, the cost at present milk prices is about $60 million. Undetected subclinical ketosis probably costs at least as much. If treatment, prevention, and other costs could be determined, an annual loss approaching $150 million for US dairymen is probable.

Lactation ketosis will be difficult to eliminate. Average worldwide milk production per cow has increased 1.25% per year for 20 yr (39). Even as diets and management are improved to reduce ketosis in today's cows, future genetic improvements may continue to increase milk production and, therefore, lead to continued susceptibility of future cows (6).

Current Knowledge of Ketosis

The status of knowledge and research in ketosis was reviewed thoroughly by Shaw 25 yr ago (97) and has been updated and summarized in numerous ways since (4, 6, 7, 12, 13, 29, 39, 55, 56, 94, 95, 98).

Biochemical Changes and Clinical Signs. Signs of ketosis were recognized as easily and almost as well characterized 25 yr ago as they are today. There seems to be agreement that most cases of primary ketosis occur before 6 or 8 wk postpartum; the incidence peaks when cows approach peak lactation. Ketotic cows are usually in negative energy balance (6). Two consistent metabolic changes are decreased blood glucose concentrations from a normal of 50 to 60 to as little as 25 mg/100 ml and marked increases in concentrations of ketones in blood, urine, and milk (12, 96, 98). Blood ketones may increase from a normal of less than 10 to as high as 50 mg/100 ml as ketosis progresses. Other frequently observed changes include increases in free fatty acids and triacylglycerols of plasma (95), decrease in liver glycogen (12, 98), and increases in liver lipid (7, 12, 95, 96) that can lead to liver damage (98). In extreme cases, up to 30% of liver weight (68% of dry matter) may be lipid (96) in contrast to a normal content of about 7%.

Numerous other biochemical changes have been reported, especially by Baird and his colleagues (4, 5, 8, 9, 10, 11). Recently Baird (4) summarized data on several blood and liver metabolites. The ratio of β-hydroxybutyrate to acetoacetate in blood decreased from 10.5 for normal cows to 4.3 for spontaneously ketotic cows and to 3.6 for starved ketotic cows. Concentrations in plasma of gluconeogenic amino acids decreased whereas the branched-chain ketogenic amino acid concenration increased in starvation ketosis (4, 10). In a study with cows that developed spontaneous ketosis (10), activities of the gluconeogenic enzymes propionyl-CoA carboxylase, pyruvate carboxylase, phosphoenolpyruvate carboxykinase, and fructose-1,6 diphosphatase in the liver did not change. With lactating cows starved for 6 days, however, phosphoenolpyruvate carboxykinase activity decreased significantly (5).

Decreases in blood glucose and increases in blood ketones can be used to indicate the possibility of impending clinical ketosis; in fact, on-farm difficulties in obtaining blood plus cost to analyze samples preclude routine blood analyses as a feasible management technique. Also, ketones usually are detectable in milk and urine before clinical ketosis is manifested. Testing of milk or urine for ketones, therefore, can be a practical management technique (26, 95, 96). Detection of ketones in milk or urine is not verification of clinical ketosis, but, conversely, absence of ketones in urine is confirmation that a cow does not have ketosis.

The composition of visible signs shown by ketotic cows has been lucidly described by Fox (29) and Schultz (94, 95). The cow first begins to lose appetite, pick at her feed, and leave some grain. She may progress from leaving most of the grain and some silage to the stage of eating only small amounts of hay and preferring to eat bedding. The further the ketosis develops, the greater is the development of perverted appetite. Concurrently, milk production is decreasing, and, in severe cases, decreasing dramatically. In mild cases, the only observation may be that the cow is not "doing well." A few affected cows will show nervous symptoms (29).

Etiology of Ketosis. Specific biochemical and physiological causes of ketosis have not been proven. Baird et al. (6) postulated that there is no single cause but that an inadequate nutrient supply, especially of energy, is a major factor. Theories of ketosis development relate

to glucose deficiency as a central theme; or glucose deficiency may be the primary theory; and various subtheories may deal with possible causes of glucose deficiency. This theory is logical because 60 to 85% of the available glucose is used in the mammary gland for milk synthesis (14). There is also a strong interaction between excess fatty acid availability or mobilization and glucose deficiency. Bergman (13), in his thorough review of many interrelations between hypoglycemia and ketosis, supported the glucose deficiency theory, whereas Kronfeld (56) did not agree completely with a carbohydrate shortage theory but states that the lactational demand seems conducive to excess fat mobilization, which contributes to development of ketosis.

Shaw (97, 98) and his coworkers were early proponents of the idea that a deficiency of adrenocorticotrophic hormone (ACTH) or cortisone was a primary cause of ketosis because of definite histopathological changes in adrenal glands of ketotic cows. Although use of glucocorticoids, or various derivatives thereof, still is probably the most common treatment for lactation ketosis, Schultz (96) suggests no convincing evidence shows that ACTH or cortisone deficiency is a primary cause of ketosis. Glucocorticoid treatment promotes gluconeogenesis and thereby provides more of the critically needed glucose for the ketotic cow. Glucose demand also is reduced because of the decrease in milk secretion.

Another consideration is that a deficiency of oxaloacetic acid (OAA) in liver may be a primary cause of ketosis (8, 12, 96, 107). This theory is based upon the concept that the lactating cow has a major "drain" of glucose into milk lactose (8) and continually removes gluconeogenic intermediates, especially OAA, from liver. Bergman (12, 13) cites three possible explanations for an OAA deficiency: a) an excessive use of OAA for gluconeogenesis because of increased activity of phosphoenolpyruvate carboxykinase, b) a deficient production of OAA because of a shortage of precursors such as propionate, amino acids, or lactate, and c) an altered redox state exemplified by a greater NADH to NAD^+ ratio and consequent conversion of mitochondrial OAA to malate. Treacher et al. (107) found that glucose infusions into starved cows caused a greater increase in citric acid cycle intermediates (especially q-ketoglutarate and citrate) than in glycolytic intermediates. There also was an increased oxidation potential in hepatic cytosol. They cited references that show an increase in liver OAA and a decrease in liver phosphoenolpyruvate carboxykinase when a cortisol derivative was given to ketotic or healthy cows. Testing the OAA deficiency theory has been hampered because mitochondrial, extramitochondrial, and cellular OAA are relatively unstable and difficult to quantitate.

Another idea, which could be considered an extension of the OAA deficiency theory, is that a great mobilization of lipid overcomes the cow's capacity to oxidize fatty acids (95, 96). If a high-producing cow goes into negative energy balance, the normal response is to mobilize body reserves, mostly adipose triacylglycerois, for energy (95, 96). If glucose and, subsequently, mitochondrial OAA are limiting, then the cow cannot oxidize completely all mobilized fatty acids, and the excess is converted to ketones, which dramatically increase in blood. One unanswered question is whether excessive gluconeogenesis "drains off" OAA or whether lack of glucose does not allow sufficient OAA to combine with acetyl-CoA from fatty acid oxidation.

Prevention and Treatment. As factors that may predispose toward ketosis, Schultz (94) lists: a) glucose drain for lactose production, b) excess body fat at calving, c) inadequate energy intake after calving, d) abnormal liver function, e) endocrine disorders such as insufficient ACTH or glucocorticoids, f) deficiencies or excesses of dietary protein, g) mineral or vitamin deficiencies, and h) high intake of ketogenic materials. If ketosis is to be prevented, as many of these factors as possible should be circumvented (6, 7, 39, 94, 95, 96, 98). Schultz (95, 96) listed nine preventive recommendations: a) avoid excessive fattening before calving; b) increase concentrate intake moderately in the late dry period but as rapidly after calving as possible and maintain intake; c) feed at least one-third of the dry matter as high-quality roughage; d) avoid abrupt dietary changes, especially to poor-quality feeds; e) feed recommended amounts of protein, vitamins, and minerals; f) avoid silage high in butyric acid; g) maximize intake by providing for comfort, exercise, and absence of stress; h)

monitor milk ketones weekly for early detection; and i) select cows with vigorous appetites.

Ketosis may be either primary or secondary. Shaw (97, 98) advocated that ketosis that does not respond to glucocorticoids or glucose is secondary. With primary ketosis, body temperature does not increase (96). Causes of secondary ketosis include mastitis, metritis, displaced abomasum, indigestion, retained placenta, nephritis, hardware disease, and extended milk fever (29, 95).

Common treatments (29, 39, 94, 96) are oriented toward increasing the glucose available to the cow. Initial treatment can be to increase feed intake by offering fresh or different feeds. The emphasis should be to find a different ingredient with the regular diet.

If a cow is largely or completely anorexic, treatment usually will begin with intravenous injection of glucose or possibly fructose (29). An intramuscular injection of a glucocorticoid or of ACTH given immediately thereafter provides a sustained impetus toward gluconeogenesis (7, 20). In severe cases, further intravenous or intraperitoneal injections of glucose may be necessary to give continuing recovery. Treacher et al. (107) explained that the biochemical action of glucose relates to: a) decreasing availability of free fatty acids for hepatic oxidation, b) increasing hepatic concentrations of citrate and α-ketoglutarate, and c) increasing oxidation potential or hepatic cytosol.

Treatment with glucocorticoids has become accepted widely within the lat 25 yr, and several forms are available (20). Baird et al. (7) described metabolic changes in liver after such treatment. Sodium propionate, administered orally, was a treatment and preventive for a few years (93), but it largely has been replaced by propylene glycol (26, 96), which is also a gluconeogenic precursor but is more palatable than propionate. In the late 1960's, some evidence showed that methionine or its hydroxy-analog was useful in treatment of ketosis, but other evidence showed only minimal benefits (95, 111); usage of methionine, therefore, has not become common. Some research suggests that nicotinic acid, an antilipolytic agent, may be used to prevent or treat ketosis (30, 95, 112). Results show some potential for effective treatment of ketosis with daily intakes of 12 g of nicotinic acid (30).

Production and Use of Ketones. Progress in the biochemical understandings of ketosis has been considerable in the last 25 yr (4, 5, 8, 10, 11, 12, 21, 55, 69, 70, 96). Characteristic hyperketonemia of ketosis must be caused by changes in relative rates of disappearance and production of ketones. Many pertinent facts about enzymology of ketone metabolism and about contributions of various organs to ketone production and use were summarized succinctly by Schultz (96). Ketones in blood of lactating cows arise largely either from butyrate produced in the rumen and converted to β-hydroxybutyrate by rumen mucosa during absorption (4, 11, 12, 96) or from metabolism in liver of long-chain free fatty acids (FFA) primarily released from adipose tissue during energy deficit (4, 11, 12, 96). Schultz (96) cites reports that state that 81% of FFA taken up by liver produces ketone bodies in ketotic animals and that liver slices from ketotic ewes form ketones at rates that are 10 times the rates in normal livers. The FFA are oxidized in liver mitochondria to the normal intermediate acetoacetyl-CoA, which then can be oxidized completely to CO_2 by acetyl-CoA in the citric acid cycle or can be converted to acetoacetate by two enzymatic pathways (4, 11, 96).

The first pathway, a direct conversion to acetoacetate, is catalyzed by acetoacetyl-CoA deacylase that is present in ruminant liver and kidney but is absent, or present at low activity, in mammary gland and rumen epithelium (4, 11, 96). The physiological importance of the deacylase pathway, however, has been questioned (11). The second pathway involves two reactions and two enzymes, hydroxymethylglutaryl-CoA synthase and hydroxymethylglutaryl-CoA lyase. The synthase is in ruminant liver and rumen epithelium but seems to be absent from kidney and mammary gland (11). Thus, acetoacetate can be formed by either the deacylase or the synthase pathway in liver, by the deacylase pathway in kidney, or by the synthase pathway in rumen epithelium. Ketosis did not cause significant changes in activity of any of these ketogenic enzymes (11).

Once acetoacetate is formed, it either can decarboxylate spontaneously and irreversibly to acetone at about 5% each hour or it can be converted enzymatically to β-hydroxybutyrate by β-hydroxybutyrate dehydrogenase. The acetone enters a pool that turns over slowly and

increases in size, but not in turnover rate, as acetone concentration increases (66). Most acetone, therefore, is in urine, milk, or breath. Most β-hydroxybutyrate dehydrogenase activity of liver, kidney, and rumen epithelium is in the cytosol; in the same tissues of nonruminants, the enzyme is primarily in mitochondria (113). The enzyme, although it has low total activity in liver of fed ruminants, reversibly interconverts β-hydroxybutyrate, which is ordinarily the major ketone in blood of all species, with acetoacetate. Controls for the β-hydroxybutyrate to acetoacetate ratio with respect to cellular redox potential need much more research.

Ketones can be used by skeletal muscle, kidney, lactating mammary gland, and intestinal tissues (4). Whereas liver, brain, and rumen epithelium do not normally oxidize ketones to any great extent, β-hydroxybutyrate, although more stable than acetoacetate, must be converted to acetoacetate before it is metabolized. The acetoacetate then is activated to acetoacetyl-CoA and converted by acetoacetyl-CoA thiolase to acetyl-CoA that can be used by the citric acid cycle of for fatty acid synthesis (12, 96). In ketosis, however, there probably is a shortage of OAA for citric acid cycle oxidation, and the physiologic condition of the cow is such that fatty acid synthesis is not a major process except in the mammary gland. Interrelations between hormonal controls and ketone use in ruminants are not well defined.

Areas of Major Progress. Although progress in several areas of ketosis has been meaningful, our opinion is that there has been only limited progress in understanding, preventing, or treating ketosis in the last 25 yr. Progress has been most significant in obtaining data related to amounts of metabolites such as ketones, glucose, lipids, and volatile fatty acids entering or leaving liver, kidney, mammary gland, and gastrointestinal tract and the endocrine status of the ketotic animal. Baird, Bergman, and their respective coworkers have been instrumental in developing the necessary techniques and obtaining initial data (4, 5, 8, 12, 13). For example, Baird et al. (8) showed decreased ketogenesis from splanchnic tissues of ketotic cows. We believe that obtaining "transorgan balances" from cows in normal, initially ketotic, clinically ketotic, recovering, and recovered states offers opportunity for greatly increased understanding of lactation ketosis. In fact, these data seem essential. Such research should be pursued vigorously but will require major inputs of time, intellect, and financial resources.

Baird and his coworkers also have been instrumental in obtaining metabolite concentrations and enzyme activities in various tissues, especially liver (5, 9, 10, 11). This area is also promising for future research. We already have mentioned both the progress in understanding the enzymology of ketosis and the changes in techniques for treating and preventing ketosis.

Progress has been significant in two broad areas intimately related to lactation ketosis. The first area is ruminant gluconeogenesis or glucose metabolism (12, 13, 56, 96, 107). The second area is ruminant lipid metabolism and regulation thereof (12, 21, 96). Progress has been evident also in the area of effects and interrelations of hormones (9, 20, 55, 69, 96). Additional information in these areas, however, is needed to gain a fundamental understanding of lactation ketosis.

Progress has been considerable in understanding endocrine changes of lactation ketosis. In keeping with the glucose shortage theory, ketonemic cows have low basal insulin concentrations and show highly reduced secretion of insulin postprandially or after glucose loading (47, 48). The findings of Hove (46) that the mammary uptake of glucose seems to be independent of insulin concentrations of plasma may provide an explanation to the fact that the mammary gland can extract a major part of the glucose production at peak lactation in spite of the generally low amounts of insulin in plasma. Changes of pancreatic hormones in plasma seem to favor a low rate of glucose use in insulin-sensitive tissues and maintenance of a high rate of hepatic glucose output. In comparisons of ketotic and nonketotic cows, no major differences in either growth hormone or glucocorticoid concentrations in plasma were observed (16, 36).

Future Areas of Ketosis Research

As mentioned already, one area that seems to hold great potential is to expand upon transorgan balance studies. Only by understanding complete metabolite or energy balances for involved organs can one ever hope to

understand fully the etiology of ketosis. Hormonal changes and interactions will be much more interpretable if they can be related to metabolite balances. Baird et al. (7) showed that data on input and output of liver metabolites are needed for each situation for which data on intracellular metabolite concentrations exist.

A second area that seems to hold great potential is a biochemical approach to obtain metabolite concentrations and enzyme activities in cells and subcellular compartments of involved organs. More information is needed on hormonal control of metabolite concentrations and of ketone metabolism. Many techniques and available information on ketone metabolism in nonruminants will have to be applied to research on ketosis in cows.

A third area that seems to hold great potential is development of a functional model of clinical ketosis. If progress in the two areas just mentioned is to be made, a valid model would be extremely advantageous. Essential characteristics of spontaneous clinical ketosis that should be in a model are: a) a major and extended glucose drain, b) an extended energy deficit, c) a major increase in mobilization of body lipids or an influx of ketogenic compounds such as in high-butyrate silage, or both, d) a gradual progression from subclinical to clinical ketosis over several days, e) an increase of blood ketones that causes ketonuria, f) a marked decrease in blood glucose concentration, g) a rate of ketosis development that causes fatty livers characteristic of clinical ketosis, h) a maintenance of feed intake until ketosis causes anorexia, i) no increase in body temperature, and j) a responsiveness to treatment with either glucose or glucocorticoids. None of the many published induction schemes has met all these criteria. Being able to produce "clinical" ketosis consistently in lactating cows would be a great research advantage. An even greater research advantage might be given with respect to animal cost, surgery, and use of isotopes if a functional, nonlactating ruminant model could be developed. Such an idea is not completely unrealistic because a major complication of human diabetes is ketosis, which must not be dependent upon lactation or hormonal and metabolic changes associated therewith.

A fourth area that seems to hold great potential is whether acetate should be considered a ketone body. Early reports would argue against this concept because acetate has been reported to be glucose sparing first by Shaw (97) and then by Bergman (12), and rumen acetate was thought to be of only minor importance as a ketogenic agent (94, 96). Other reports show that, in both subclinical and clinical ketosis, blood acetate seems to be increased in proportion to the degree of ketosis (111), that blood acetate is increased in spontaneous ketosis (4), and that 40 to 50% of total acetate may be from net production by liver (4). Baird (4) reported that blood acetate is decreased in starvation ketosis, and Kronfeld (54) speculated that decreased acetate entry rates associated with spontaneous ketosis represent effects of being anorexic for several days. Transorgan balances of acetate across the liver and gut could resolve this question.

There are other questions to be answered. Are interrelationships of malonyl-CoA and carnitine concentrations in liver mitochondria and in cytosol a significant part of the cause of lactation ketosis as in ketosis in nonruminants (69, 70, 71)? How is fatty acid oxidation controlled in livers of lactating cows? What are the interrelations of propionate with gluconeogenesis and energy metabolism in ketosis, and can ketosis be eliminated from cows producing large quantities of milk? Lactation ketosis is costly; there is much more to be learned, and such urgently needed knowledge will not be obtained easily or inexpensively.

MILK FEVER

Milk fever is an afebrile hypocalcemic disease of cattle usually associated with parturition and initiation of lactation. A number of reviews and discussions are available concerning parturient hypocalcemia (3, 19, 40, 49, 57, 58, 61, 62, 63, 65, 67, 74, 77, 79, 105, 114). This disease has been known by a number of terms including parturient paresis, milk fever, parturient apoplexy, eclampsia, and paresis peurperalis. The term "parturient hypocalcemia" (PH) (3) will be used here to refer to the classic clinical syndrome.

Importance

The cost of PH in Sweden was estimated in 1969 to be at least 10 million Swedish crowns

annually (49). Payne, in 1966, listed the national estimate of depreciation due to PH in Great Britain at 161,000 pounds annually (78). The annual loss from PH in the United States was estimated to be approximately $10.5 million in 1965 (62). Estimates of losses appear to be much too low if losses had been evaluated as previously reported by Leech et al. (60). They reported that cows that have had the disease depreciated by an average of 35 pounds in market value and also suffered a marked reduction in productive life. In France, 150,000 cases of PH were reported in 1959, and a 10-million franc loss was estimated (59).

Losses from this disease are difficult to quantitate because of the many indirect costs. For example, some owners cull older, high-producing cows from a herd (especially Jersey herds) because of a history of repeated cases of PH. Premature loss of these excellent blood lines can have considerable effect on future herd milk production. Also, some dairymen do not feed alfalfa silage for a few weeks before parturition because of the increased incidence of PH when cows consume this feed even though it may be the most logical and economic forage available. Although cows may be treated successfully for PH, secondary complications (degeneration and necrosis of muscle, nerve paralysis, split pelvis, ruptured gastrocnemius tendons, mastitis, and ketosis) may result in ultimate culling or death of the cow. In addition, dairymen may not completely milk their cows for several days postpartum in an effort to reduce the incidence of PH. This practice can increase incidence of mastitis and decrease milk production. Also, many dairymen supplement diets with special mineral supplements in an effort to avoid PH. Thus, even though some owners report a low incidence of PH, many costly measures are used in an attempt to manage "around" the disease. The dubious practices normally are not counted as a true cost associated with the disease.

By any measure, PH costs the dairy industry many millions of dollars each year and, therefore, is of considerable economic significance.

Current Knowledge of Parturient Hypocalcemia

Breed and Age Effect on Incidence. We generally accept the fact that there is a breed difference in incidence of PH; incidence is highest in the Jersey breed (62). Parturient hypocalcemia is uncommon before the third parturition, and incidence is highest at the fifth or sixth parturition. Thus, cows are most likely to develop PH during their most productive years (61).

Biochemical Changes Associated with Parturient Hypocalcemia. We have recognized for years that most cows, regardless of whether they develop clinical signs of PH, have some degree of hypocalcemia associated with parturition (58). Only in cows developing severe hypocalcemia do overt clinical signs of PH occur. Most cases of PH develop within 24 h of parturition. Both total calcium (Ca) and ionized plasma calcium concentrations decrease. Other changes associated with PH have been reviewed (17, 62). They are hypophosphatemia, hypermagnesemia, hyperglycemia, hypomagnesemia, and hypoinsulinemia. Also, plasma concentrations of urea nitrogen, lactic acid, pyruvic acid, chloride, hydrocortisone, glutamicoxalocetic transaminase, parathyroid hormone (PTH), and $1,25\text{-}(OH)_2D_3$ increase, as does hematocrit. Blood concentrations of total inorganic phosphorus (P), total P, total acid-soluble P, lipid P, and globulins decrease, as does carbon dioxide capacity. Body temperature commonly decreases in cows with severe PH, especially in cool environments (58). Extremities, especially ears and teats, may feel cold even though rectal temperature is not decreased.

The period in which Ca homeostasis is challenged most severely and is most subject to failure is at the time the udder initially fills with milk and lactation is begun. Lactational demands for Ca exceed that of gestation by a factor of 2 to 5 (62). Near parturition, inflow of Ca from the diet is temporarily insufficient to provide the Ca that is secreted into the milk, and all cows develop a temporary decrease in outflow of Ca from bone as part of the initial adjustment to lactation. The reason for this decrease in outflow of Ca from bone is unknown (67).

The most important long response needed at initiation of lactation is an adequate increase in dietary Ca inflow (67). Increased intake and net absorption of Ca must be the major long adaption to increased Ca demands of lactation if severe depletion of bone mineral is to be

avoided during the lactational cycle. However, severe disruption in dietary input of Ca is common, especially in older cows, because of the inappetance frequently associated with parturition (62). This inappetance and the lag period before net absorption of gut Ca can be increased create the need for a readily available bone reserve of Ca if calcium homeostasis is to be maintained. However, dietary Ca intake of dairy cows during gestation is commonly much greater than Ca demands. Consequently, during this period, bone mineral reserves of Ca are not contributing greatly to maintenance of Ca homeostasis. Thus, bone tissue during this period is inactive (114). As a result, relatively little target tissue is present to respond to hormonal signals generated when Ca homeostasis is perturbed by the great Ca demands of lactation. Consequently, the "lag period" is several days before necessary changes activate bone tissue to serve as an effective Ca reserve.

Prevention of Parturient Hypocalcemia. To provide for a responsive, effective bone reserve of Ca at initiation of lactation, special procedures have been developed to prepare this tissue (62). One effective method is to feed a low Ca diet at least 5 days before parturition (18, 32, 33). This procedure causes a slight hypocalcemia and increased secretion of parathyroid hormone (PTH) and 1,25-$(OH)_2$D. Under continued stimulation of these two hormones, bone tissue is prepared to meet much of the Ca demands of lactation so that severe hypocalcemia and clinical signs of PH do not develop. Several days of stimulation apparently are needed to prepare the bone adequately as judged by plasma hydroxyproline concentration (33).

Attempts have been made since 1930 to prevent PH by administering large amounts of vitamin D (19, 41, 42, 43, 51). Much more vitamin D is required if given orally than if given parenterally to prevent PH or to induce vitamin D toxicity. This discrepancy could be explained in part by degradation of modification of vitamin D in the rumen. Feeding 5×10^6 IU D_2 or less per day for 2 to 4 wk prepartum (42) or parenterally giving 5×10^6 D_3 or less 2 to 4 wk prepartum did not prevent PH. Indeed, prepartum doses of 2.5 to 5×10^6 IU D_3 given parenterally induced PH, possibly by interfering with normal 1,25-$(OH)_2$D production during the early postpartum hypocalcemic period (64).

Feeding of larger amounts of vitamin D (20 to 30×10^6 IU/day) 3 to 8 days prepartum or 32,000 IU/day throughout the year effectively prevented PH in cows with a previous history of PH (41, 42). Injections of 10×10^6 IU D_3 about 1 wk prepartum also reduced incidence of PH in cows with a previous history of PH (80). Injection of more than 10×10^6 IU D_3 during the last 10 days of parturition may result in clinical and pathologic toxicity (22, 80). Injections of 15 to 20×10^6 IU D_3 in divided doses given 30 days prepartum to Jersey cows were highly toxic and resulted in 80% mortality (64). That such doses of vitamin D_3 did not produce signs of toxicity in nonpregnant Jersey cows shows that pregnancy is associated with a reduced tolerance to vitamin D. Feeding low-calcium diets reduced toxicity of vitamin D (32, 80, 90). Lack of documented toxicity of some amounts of vitamin D recommended to prevent PH can be explained in part by the short time commonly between vitamin D administration, parturition, and initiation of lactation with its greatly increased Ca demand.

Results of recent work (45) show that massive parenteral dosage of vitamin D_3 to cows leads to an increase in plasma 1,25-$(OH)_2$D about 2 wk after administration. The increase in 1,25-$(OH)_2$D persists at least 1 to 3 weeks, depending on the amount of D_3 given. Also, the maximum hypercalcemia and increase in plasma hydroxyproline (an indicator of bone resorption) were greatest about 4 to 5 wk after injection. From 10 to 20 million units were injected 30 days prepartum in efforts to use the period of maximum increase in plasma 1,25-$(OH)_2$D, calcium, and hydroxyproline as the optimal period in which to initiate lactation. This treatment maximized toxicity of these injections as well as minimized postpartum hypocalcemia. Other recent work (85) indicated that vitamin D_3 injected 2 or 3 days before parturition caused a transient increase in plasma 1,25-$(OH)_2$D the day following injection. This release of 1,25-$(OH)_2$D was postulated as responsible for the preventive action of vitamin D_3 for PH. Use of 25-OHD (91) and other vitamin D metabolites to prevent PH would be limited by factors similar to those that limit the use of vitamin D.

Treatment of Parturient Hypocalcemia. Methods to treat cows with PH have been reviewed (62). In general, treatment of PH is

designed to reverse depressed neuromuscular transmission, to correct paresis, and to maintain the cow until normal calcium homeostasis can be reestablished through increased Ca input via the gut and bone. Various types of calcium preparations and methods of administration (IV, IV plus SQ) have been developed over the years to increase effectiveness of treatment (58). If simple, uncomplicated PH is present, there does not seem to be any marked advantage of using alternative routes of administration or addition of other compounds to a solution of 23% calcium borogluconate given IV.

On an experimental basis, 1,25-$(OH)_2D_3$ or 1α-D seems to hold promise in reducing incidence of relapse after treatment (91, 92). The time sequence of the usual postpartum hypocalcemic period of cows is such that it takes 1 to 2 days for cows to reach minimum blood Ca concentration and 2 to 3 days for blood Ca concentration to stabilize near the normal range. Thus, logically, Ca infusions (which usually only increase blood Ca concentrations 6 to 8 h) will be followed by fewer relapses if given after cows have reached minimum blood Ca concentrations and concentrations are stabilized or increasing slowly. This result has been shown (28, 62). The Ca treatment itself seems to have minimal effects on decreasing the time required to restore normal blood Ca concentrations permanently; it is used more to sustain the animal until the normal means of restoring blood Ca become effective.

Insufflation of the udder is also an effective treatment for PH (58, 67). This promotes a gradual and moderate rise in blood Ca concentrations by reducing milk formation for as long as 24 h and also may promote transfer of some Ca from milk or udder back into circulation (62). This is one of the few treatments that affects Ca outflow into the udder and to milk rather than increases Ca input. Induction of mastitis after insufflation is possible without great care.

Cows that do not respond favorably to commonly used Ca therapy often are referred to as downers, alert downer, or atypical milk fever, or creeper cows (50, 62). They are characterized by prolonged periods of recumbency and usually have a variety of secondary complications (50).

Future Areas of Parturient Hypocalcemia Research

Detailed knowledge of biochemical, hormone receptor, and cellular changes in the bone, gut, and kidney of cows during the peripartal period is essential to devise the most effective methods to prevent PH. The traditional approach to the control of PH is to increase the Ca input in the system; however, it is possible that control measures based on control of Ca outflow into the mammary gland and milk may be effective (85, 86). Development of the latter approach has to await characterization of mechanisms of Ca transport from blood to mammary tissue and milk.

Feeding a Ca-binding resin that resists rumen degradation would seem an effective way to provide an anticipatory stimulant to bone Ca mobilization before parturition. However, practical considerations of providing a well-controlled intake over a short period to a minority of dry cows in the herd drastically limits practicality of such a measure.

Measures to prevent loss of appetite or to increase appetite near time of parturition would be one of the most direct and effective ways to increase Ca input into the system. A better understanding of appetite control of ruminants is needed.

Correction of an obvious Ca or P oversupply during the dry period is the first step in preventing PH in a problem herd. This usually will reduce greatly the incidence of PH in the herd. In efforts to eliminate other cases of PH, a diet extremely low in Ca and limited in P is effective but may not be practical under many management conditions. In California, many herds consume prepartal diets high in Ca, but for unexplained reasons, there are few herds with a high incidence of PH. It is doubtful that any practical protective measure will be developed that can be applied uniformly to all dry cows. A more practical approach would be to treat only cows that the owner suspects will develop PH, especially those with a previous history of PH. A standard treatment with vitamin D_3 or 25-OHD_3 which ignores age, breed, weight, diet, and management probably will not prevent PH effectively without serious side effects.

The most effective control of PH probably will be a method that includes an increase of Ca input into the system as well as control of

output of Ca into milk such that a steady state can be maintained throughout the peripartal period. For PH preventive programs to be effective, they likely will have to be designed specifically for groups of dairy herds with similar management practices.

Mimicking adaption of cows to initiation of lactation will probably be the most effective and nontoxic way to prepare prepartum cows for sudden initiation of lactation. If this concept is correct, then one would predict that feeding cows during the immediate prepartum period a diet as low in Ca and P as is practical, possibly in concert with treatment of the cow for several days prepartum with PTH and 1,25-$(OH)_2D_3$ or substances that mimic their actions, would be the most effective method of preventing PH. Variability of time of parturition often necessitates prolongation of a particular preventive practice; thus, methods with the least detrimental side effects are most likely to be used.

The use of other more active metabolites and analogs of vitamin D also has been studied both for treatment and prevention of PH (31, 44, 48, 91). In general, these compounds seem promising. They have the advantage of a shorter biological life, so toxicity problems are reduced; however, because of the variability of the time of parturition in cows, multiple doses may be needed adequately to protect cows against PH. Most biologically active vitamin D compounds, including 1α-vitamin D_3, would be expected to cause prolonged hypercalcemia and hyperphosphatemia. This response would result in inhibition of the 1-hydroxylase which would lead to lowered endogenous production of 1,25-$(OH)_2D$. Prolonged hypercalcemia also would inhibit PTH secretion. The combination of decreased 1,25-$(OH)_2D$ and PTH would cause the cow to be susceptible to hypocalcemia when the exogenous supply of material with vitamin D activity was stopped. It would take several days to reinstitute normal 1,25-$(OH)_2D$ and PTH secretion even with severe hypocalcemia. These changes will make proper timing of administration of the prophylactic substance important and present a substantial problem to their widespread use as PH actually could be induced in cows with these treatments. Many of the natural and probably many of the synthetic vitamin D metabolites are transported into milk but would be expected to be cleared from the system rapidly as blood contents decrease. New natural vitamin D metabolites and potent synthetic vitamin D analogs are being discovered. Thus, the potential of finding an effective, nontoxic compound that will have use in an overall management program to prevent PH seems promising. Some of the problems that must be overcome before these compounds prove practical are: development of slow-release forms for parenteral and oral use (bypass rumen), production of these at reasonable cost per dose, governmental clearance for use in cows producing milk for human consumption, development of a practical and effective means of administration under the great variety of diet and management conditions used in the dairy industry, and induction of PH if dosage is inadequate. However, stimulating only one limb of the calcium homeostatis mechanism will not likely by the most effective method for preventing PH.

GRASS TETANY

Importance

Grass tetany (GT) is a major problem of grazing cattle and sheep in the temperate regions of the world. A number of clinical diseases are included in GT: "Kopziekte" or grass tetany in cows, sheep, and goats as seen in The Netherlands and Belgium; lactation tetany in Great Britain; grass staggers in New Zealand; tetany of cattle grazing other small grains such as wheat, rye, and oats; winter tetany, and milk tetany of calves (65).

Current Knowledge of Grass Tetany

A number of excellent and extensive reviews deal with the soil, forage, and animal factors in GT (1, 15, 23, 27, 30, 34, 35, 38, 63, 65, 87, 99, 100, 103, 105, 109, 110).

Grass tetany is a disease affecting cattle and sheep not receiving adequate available Mg. The low availablity of Mg in forage may be from either low Mg concentrations or to factors in the forage that reduce availability of Mg to the animal (34). Older, lactating cows and ewes are most susceptible (63), but the disease also has been reported in calves and steers (63).

Types of Grass Tetany. Grass tetany has been classified into three main types based on diet and season (103). The spring type affects lactating cows a few days after they are put out

on grass. The winter type affects cattle fed winter rations in confinement. The out-winter type affects cattle in late winter that have been maintained thoughout the winter on sparse pasture plus some supplemental hay.

Grass tetany also has been classified by clinical types (87). The most common type is the tetanic syndrome type, which is characterized by nervousness, muscle twitching, ataxia, convulsions, recumbency with spasms, and opisthotonos. The paretic type is characterized by listlessness, staggering, paresis, recumbency, and coma without spasms. Subclinical types occur that are associated with depression of appetite and milk yield, slight nervousness, anemia, and udder edema.

In a review of the classification of GT, clinical signs associated with ataxic and recumbent cases of "metabolic disorders" have been correlated with concentrations of Ca and Mg in blood (64). Disorders were classified into "milk fever" types and "grass tetany" types of syndromes. Combinations of changes in blood were: a) hypocalcemia combined with hypermagnesemia; b) hypocalcemia combined with normal magnesemia; c) hypocalcemia combined with hypomagnesemia; and d) normal calcemia combined with hypomagnesemia. The first two types (milk fever) were characterized by gut stasis, paresis, coma, and low body temperature; the last two types (grass tetany) were characterized by excitement, tetany, and convulsions. Concentration of blood Ca seems to be the distinguishing feature in the milk fever type of disease, and concentration of blood Mg seems to be the distinguishing feature in the GT type of disease. Ender et al. (27) pointed out that hypocalcemia was not a prerequisite for clinical signs of GT. Swan and Jamieson (104) described hypomagnesemic and normocalcemic cows that did not have obvious signs of disease; however, the cows developed severe clinical signs of tetany if stimulated by handling. An intermediate type of disease was described by Udall (108) in which beef cows developed low blood Ca and Mg and violent tetany near parturition. The cows responded to treatment with calcium gluconate.

Factors that Influence Development of GT. Numerous investigators have concluded that marked decreases in blood Mg concentrations seem to be the primary predisposing factor for GT. Availability of dietary Mg has ranged from 5 to 40% (89). Reports concerning sites of Mg absorption were reviewed (63). Magnesium seems to be absorbed from most areas of the gastrointestinal tract; however, net absorption is thought to be greatest in the rumen, reticulum, and possibly omasum and colon. The amount of Mg absorbed at a particular site does not seem to be related specifically to metabolic requirements for Mg but to intraluminal concentration of available Mg at a given site. The percentage of Mg absorbed from the gut is relatively small as compared with the amount of Mg ingested; however, when dietary Mg is adequate, the amount of Mg absorbed is large as compared with metabolic needs for Mg. Individual cows most prone to hypomagnesemia have a reduced ability to absorb Mg from the gut (89). Many parts of the small intestine have net secretion of Mg. Potassium ions have a marked inhibition on Mg transport across the rumen wall. Thus, a forage high in K and low in Na (and the decrease of the Na/K ratio in the saliva that results from consumption of these types of forage) could have profound effects on Mg transport in forestomachs of ruminants and contribute greatly to the pathogenesis of GT.

Binding of Mg and Ca by organic material in digesta may have significant effects on Mg and Ca absorption. One factor influencing Mg availability for absorption that has not been investigated in detail is the incorporation of Mg into rumen microbes (63).

Head and Rook (37) suggested that high ruminal ammonia concentrations decreased availability of Mg in forage. They found that the availability of ingested Mg decreased when rumen ammonia concentrations were increased in a cow fed hay and concentrate. Drastically reduced ultrafilterable Mg concentrations were found in the small intestine of sheep when the ration was changed from hay and concentrate to cut grass rich in crude protein. They concluded that some association existed between the low availability of Mg from spring herbage and the presence of continuously high concentrations of ammonia in the rumen.

Marked reduction in food intake decreases the ability of cows to maintain Mg and Ca homeostasis (27), especially in lactating animals (63). Kidneys contribute to conservation of Mg under conditions of hypomagnesemia and, thus, play an important role in Mg homeostasis. Sjollema (100) reported that urinary Mg

concentrations of less than 1 mg/100 ml were typical of cows with GT. This decrease in urinary Mg has been observed by many workers and it is thought to be more indicative of the Mg status of cows than is blood Mg concentration. This concept was strengthened when Rook et al. (88) reported decreased urinary Mg concentrations before serum Mg had decreased below 1.8 mg/100 ml, which is thought to be the renal threshold for Mg.

Biochemical Changes in Animals with GT. Much attention has been given to concomitant changes in blood Ca concentrations in cows with GT (38, 101, 109). In most instances, changes in blood Ca concentrations seem to be of pivotal pathophysiologic importance in development of GT.

Few studies have been of endocrine changes in cows developing GT (62, 63, 65). Apparently, appropriate parathyroid hormone (PTH) increases in blood may not be sustained as the hypomagnesemic-hypocalcemic type of grass tetany develops. However, blood PTH concentrations appropriately increase in cows developing wheat pasture poisoning (WPP), in which hypocalcemia is the predominant change, and blood Mg concentrations decrease only modestly. Plasma concentrations of the active metabolite of vitamin D, 1,25-$(OH)_2$D, seem to increase appropriately in cows affected with both GT and WPP (65).

The pathophysiologic basis of the hypocalcemia in classic GT and in WPP is not clear. Forages consumed by cows developing these conditions have been reported to be relatively low in Ca content as well as in Mg content or availability. Also, investigators have suggested that availability of Ca from bone reserves of animals with either GT or WPP may markedly decrease, as indicated by a progressive decrease in blood hydroxyproline concentrations in animals grazing these forages (65). Deficiency of Mg or inappropriately low PTH, or both, may lead to a refractory condition of bones such that they cannot function as an effective source of Ca even when severe hypocalcemia develops. If both dietary and bone sources of Ca and Mg are reduced in the face of a relatively large lactational demand for Ca and Mg, it is not surprising that there is an acute disruption of normal Ca and Mg homeostasis. The marginal supply of dietary Ca and Mg of animals grazing tetany-prone forage may be reduced for many reasons, such as rapid growth of forage, inappetance, or interruption in supply of supplemented Ca or Mg.

In most GT cases acute decreases in blood Ca are associated with development of clinical signs of either GT or WPP. Usually relatively few cows in grazing herds show clinical signs of the disease even though a large percentage may have decreases in blood Mg and Ca concentrations equal to or greater than those of cows showing clinical signs. Investigators have reported that decreases of Mg concentrations in cerebrospinal fluid (CSF) are associated more closely with development of clinical signs of GT than are blood Mg concentrations (2, 72, 73). They suggest that decreases in CSF Mg in cows and sheep with GT reflect inadequate maintenance of the proper ionic concentrations (Mg) in the interstitial fluid of the central nervous system (CSN), which leads to abnormal CSN function. These findings show that GT may be primarily the result of altered CNS function rather than a disturbance in function of the peripheral nervous system, which seems to be the case in milk fever.

Gross, Histologic, and Subcellular Changes in Cattle with GT. Gross, histologic, and subcellular pathology of the various forms of GT were reviewed (63). Four principal types of lesions were described: a) hemorrhagic, b) vascular, c) deposition of Ca salts, and d) degeneration of parenchymatous organs. Widespread vascular lesions, hemorrhagic edema, and calcification in cows with GT may alter transport of Mg into the CNS and other functions also and may explain some of the clinical signs and pathogenesis of GT. Extent and reversibility of these lesions at the time of treatment may influence the effectiveness of treatment and final outcome of the disease. DeGroot (25) described alterations in the ECG of adult cattle which were still present up to 6 mo after a hypomagnesemic episode. He ascribed these long changes to calcification in the heart.

Neuromuscular Transmission in Animals with GT. Todd and Horvath (106) found that neuromuscular transmission was facilitated and that current required to cause muscle contraction was reduced in calves with clinical signs of hypomagnesemia. Kolb (53) found large decreases in the Mg in heart, muscle, and other organs from cows with GT. Most tissues from these cows also had decreased concen-

trations of Ca, and some had decreased concentrations of K.

Treatment of Animals with GT. The usual treatment of GT is parenteral administration of Mg and Ca salts in various combinations. Treatments given soon after development of clinical signs are more likely to be effective than those given later. Commonly, 30% or more of the treated animals die (63). Irreversible changes and death may follow soon after clinical signs develop. Many days are required after treatment before plasma Ca and Mg stabilize within the normal range (65). The delay in restoring normal Ca and Mg homeostasis may be the result of a continued poor responsiveness of target tissues, or perhaps blood constituents such as Ca and Mg are reflecting only slow changes in the forage being consumed. A combination of these two processes is most likely.

Future Areas of Grass Tetany Research

The lack of a readily available reserve of large amounts of Mg in the body necessitates a constant (almost daily) input of Mg to meet the Mg demands (especially those of late pregnancy and during lactation). Any prolonged disruption of this input of Mg may result in clinical signs of GT. Thus, further research concerning the soil, plant, microbial, and animal factors affecting availability of dietary Mg for transport into the body seems of paramount importance for control of this disease. Specific areas deserving attention are the K-Mg transport interrelationship in rumen, reticulum, and possibly omasum, and the influence of aluminum on gut transport of K. Effective systems need to be developed to insure delivery of constant and adequate amounts of Mg on a daily basis to cattle under a variety of management and grazing conditions. Definitive information of the Mg requirements of cattle is not currently available. Thus, many cattle producers are either undersupplementing or oversupplementing Mg. Effects of chronic subclinical hypomagnesemia on fertility, growth, longevity, and milk production need to be quantitated to be sure that significant unrecognized losses are not occurring in the millions of cattle subjected to low Mg diets and consequent hypomagnesemia each year. Also, we need to determine whether diets relatively low in Mg are really detrimental to certain types of cattle operations; if not, then the cattle producer can avoid some of the expensive supplementation of cattle feeds with Mg which currently is costing millions of dollars each year.

The basic mechanism by which low Mg or Ca concentrations cause clinical signs of GT is not known. If this mechanism is found, we may be able to increase an animal's resistance to tetany with drugs or chemicals during the tetany season. Also, more effective and long-lasting treatments of affected cattle need to be devised. We need to develop a reliable method of predicting tetany-prone conditions of plants and animals so corrective measures are instituted only for real danger of tetany.

DOWNER COW COMPLEX

Importance

To aid in a general discussion of the peripartum diseases of the dairy cow, and because many of these diseases are interrelated with one another, they have been grouped under the general title "downer cow complex." The so-called "downer cow" in the past was often the result of some complication of PH (63).

Downer cows have to developed in 15 to 25% of the cows treated for milk fever (63). The increase in incidence of this complex has increased during the last 20 yr as management (particularly nutritional management) has been changed from focusing on the individual cow to focusing on large groups of cows (52, 68). Group feeding of dry and lactating cows promotes overfeeding of dry cows (24, 68). These overconditioned dry cows have increased susceptibility to a variety of metabolic and infectious diseases, and they are more prone to calving problems than properly conditioned cows (75).

Commonly, many cows affected with one or more of the diseases in this complex of peripartal diseases are overconditioned. Fat cows show increased susceptibility to a number of peripartal diseases such as milk fever, ketosis, digestive disorders (i.e., displaced abomasums, etc.), retained fetal membranes and metritis, mastitis, and foot problems (75, 76). The incidence of morbidity (50 to 90%) and mortality (60%) often is high in fresh cows in affected herds (34). In one 600-cow herd,

morbidity was 82% and mortality was 25% (29 of 120 cows) occurring over 4 mo. In addition, ketosis was in 38%, and retention of fetal membranes was in 62% of affected cows (76).

Current Knowledge of Downer Cow Complex

Terms used to describe these various syndromes are "downers", "alert downers", "atypical milk fever" or "creeper cows" (63), and fat cow syndrome (FCS) (75, 76). Downer cow diseases are complications resulting from PH with demonstrable muscle, tendon, or nerve injuries (63). Other syndromes in this disease complex are not as easy to characterize. Indeed, various combinations of diseases may be in the same cow.

An individual overconditioned dry cow may go through the entire FCS, which consists of: foot abscesses before calving, parturient hypocalcemia near the time of calving, retained placenta, metritis, inappetance, severe ketosis, diarrhea with or without displacement of the abomasum, and mastitis a few days postpartum. The prognosis is poor with such complicated cases, even with extensive long treatment. When FCS begins in a herd of cows, it is extremely difficult to prevent most overconditioned dry cows in the herd from also developing similar problems. Several months of proper management are required to get overconditioned cows into a physical condition associated with a low incidence of FCS.

Low milk production and prolonged calving intervals also promote FCS. Feeding excessive quantities of concentrates after peak lactation or during the dry period, combined with free-choice feeding of corn silage or high-quality hay, predisposes a herd to development of FCS (75, 76). Likewise, either underfeeding of protein or an early decrease in milk production, combined with free-choice feeding of corn silage, contributes to excessive intake of energy and overconditioning of cows (76).

In support of these findings, cows that were overconditioned during the dry period and fed a ration of 15% crude protein had a 69.4% incidence of metabolic diseases and a 31% incidence of the alert downer cows. In contrast, dry cows fed only an 8% crude protein ration had a 7% metabolic disease incidence and no alert downers. The downers commonly showed myocardosis, hepatic and renal fatty degeneration, ulceration of the abomasum, and general necrosis of muscle and uterine tissue; however, the plasma mineral changes were not different from those of unaffected cows (52).

Cows affected with FCS may develop leukopenia and decreased hepatic function (76). Low cholesterol concentration in serum (less than 100 mg/100 ml) 8 wk before calving was associated with a 70% incidence of FCS in a German study (102).

Severe fatty liver (more than 30% fat in the liver parenchyma) is mainly a response to fat mobilization from adipose tissue (89). Cows that develop fatty liver often also have a history of fertility problems in the previous lactation (84). It has been suggested (81) that development of a fatty liver can result from: a) increased hepatic lipogenesis, b) increased mobilization of FFA from adipose tissue, c) decreased hepatic oxidation of fatty acids, or d) an impaired triglyceride secretory mechanism. However, only factors b and d were thought to be part of the pathogenesis of fatty livers associated with starvation (81). High-producing cows normally lose weight during early lactation. They mobilize relatively more energy than protein from body stores to supply the energy and amino acids for milk production. The additional energy, especially protein, to meet the cow's needs must be supplied by the diet if milk production is to peak without development of a metabolic disease. Demands for peak milk production at 4 to 10 wk postpartum may increase nutrient requirements 300 to 700%. Because intake of dry matter does not reach its maximum until after milk production peaks, feed intake lags behind milk production even though feeding may follow recommended guidelines. Thus, heavy-producing cows commonly draw upon body stores during this period (24).

Experiments with fasted cows have provided some insight into mechanisms that might lead to fatty livers under these circumstances (82, 83). Hepatic uptake of FFA increases in fasted cows as a result of an increased transport of FFA to the liver with no change in hepatic extraction of FFA. Livers of fasted cows also have a net uptake rather than a net output of triacylglycerol. This net uptake probably is the result of decreased secretion of triacylglycerol. Consequently, these two factors, increased hepatic uptake of FFA and inadequate hepatic secretion of tricylglycerol, may be responsible

for development of fatty liver in fasted or underfed cows (82, 83).

Future Areas of Downer Cow Complex Research

Control of many of the diseases in this complex clearly lies in proper management of the cows after peak milk production and during the dry period. Treatment of cows severely affected with fat cow syndrome is expensive, time consuming, and often ineffective. More effective treatments need to be devised. Practical control of these diseases must be effected through management.

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