ABSTRACT

Bovine ketosis typically occurs in early lactation. Clinical signs include diminished appetite, decreased milk production, loss of weight, hypoglycemia, and hyperketonemia. Susceptibility to ketosis is probably due to the combination of appetite limitation and a high degree of precedence given to the demand of the mammary gland for nutrients, in particular glucose. The precipitating cause is likely to be development of a marked imbalance between glucose supply and glucose requirement. This imbalance then leads to decreased carbohydrate status, decreased insulin secretion, increased fat mobilization, and increased hepatic ketogenesis. Hepatic ketogenesis may be augmented by the diminished carbohydrate status. The role of hormones other than insulin in the etiology of ketosis, although probably important, has not yet been elucidated satisfactorily. Treatment of ketosis involves increasing glucose supply relative to glucose demand. Incidence of clinical ketosis can be minimized by correct nutrition and management as outlined in recommended guidelines. Besides decreasing milk yield, clinical ketosis may affect productivity adversely in other ways, for example, by impairing fertility. Subclinical ketosis is important because it may remain undetected and have effects on productivity which parallel those elicited by clinical ketosis. Future research should be directed toward understanding mechanisms conferring priority on milk production and regulating appetite.

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tion reveals that hepatic concentrations of several intermediates of the gluconeogenic pathway, both at the level of the tricarboxylic acid cycle (TCA cycle) and of the Embden-Meyerhof pathway, are decreased substantially to below normal. The reduced partners of cytoplasmic redox pairs are at greater concentrations than normal, however, indicating an increase in the degree of cytoplasmic reduction (3). These previous observations support the concept that in primary bovine ketosis there are increases in rates of adipose tissue mobilization and of hepatic ketogenesis and that these increased rates are in conjunction with decreases in blood glucose concentration and in hepatic carbohydrate sufficiency.

Ketosis may remit spontaneously. With or without treatment, exposure to clinical or subclinical ketosis is likely to ensure that maximum potential milk production will not be achieved. Whereas the most obvious effects of the disorder are the immediate ones, there also may be long-term implications for productivity. Some of these are discussed later.

Etiology

Situation in the Healthy Cow. Although few, if any, definitive experiments have been in this area, it seems probable that the key factor in rendering dairy cows susceptible to spontaneous ketosis is the metabolic priority given to the demands of milk production at a time when appetite is limited. This priority is evident because nutrient intake during this period is frequently insufficient to meet the combined metabolic demands of maintenance and milk output, so that the animal is in negative energy balance (72). Body tissue is mobilized, therefore, to support milk output. A consequence of the priority assigned to milk production is that the milk also must have priority in its demand for glucose, because the requirement by udder for glucose per unit of milk produced varies little under a wide variety of conditions (e.g., 41).

Assignment of priority to demands of milk production in early lactation is probably the result of the pattern of hormone secretion during the periparturient period. Bauman and Currie distinguished between the roles of "homeorhetic" hormones, such as prolactin, which coordinate metabolic processes to achieve and sustain a given physiological state, and "homeostatic" hormones, such as insulin and glucagon, which regulate the metabolic environment short term (12). The homeorhetic hormones probably ensure that the supply of nutrients is increased during lactation and that the mammary gland has first priority on this supply. These functions seem to be most pronounced during early lactation, which suggests that homeorhetic hormones are likely to be influential in the etiology of bovine ketosis. Effects of homeorhetic hormones may be achieved, at least in part, by modulation of the action of homeostatic hormones. For example, it is of advantage during early lactation that adipose tissue be mobilized to provide milk triacylglycerol, and, in the rat at least, prolactin encourages this process by inhibiting lipoprotein lipase (EC 3.1.1.34) in adipose tissue and stimulating the enzyme in mammary gland (75). One reason for the effect on adipose tissue may be that prolactin renders this tissue less responsive to insulin (24). Glucose also fails to inhibit the in vitro release of NEFA from adipose tissue from dairy cows in early lactation, even if insulin is present (49).

Another factor that could be of importance in ensuring that the mammary gland of the dairy cow receives an adequate supply of nutrients during early lactation is that the concentration and secretory response of insulin are low at this time (34, 44). This feature of early lactation could arise as a result of the intervention of a homeorhetic hormone, e.g., by direct action of the latter on the pancreas. Alternatively, it could arise simply because circulating glucose concentrations tend to be low, presumably as a consequence of the high glucose demand of the mammary gland. Whatever the etiology, the low insulin concentration will encourage mobilization of lipid, irrespective of any modulating effect of prolactin, and also mobilization of gluconeogenic amino acids. Furthermore, it will promote passively a high rate of hepatic gluconeogenesis. More nutrients, therefore, will be made available to support lactation. Apart from these considerations, however, the low insulin concentration may confer priority on the glucose demand of the mammary gland because current evidence indicates that glucose transport into the gland does not require insulin (33, 40, 60). Without such an insulin requirement the gland will be able to
compete successfully for glucose with other organs which do require insulin for glucose uptake.

**Sequence of Events in Development of Clinical Ketosis.** The precipitating cause of clinical ketosis is probably the severe carbohydrate insufficiency that develops when a susceptible animal attempts to maintain milk output in the presence of a marked deficiency in glucose supply. This view receives some support from the observation that subjecting lactating dairy cows to a 6-day fast will produce severe hypoglycemia and hyperketonemia if the cows are within the period of maximum susceptibility to primary ketosis (27) but not if they are outside this period. One reason for the difference seems to be that while milk output of all animals declines in response to the fast, output of cows in early lactation declines more slowly (4). In fed and initially normal animals, deficiency in glucose supply could arise as a result of inadequacies in availability of gluconeogenic precursors, including endogenously-derived gluconeogenic amino acids, or in the mechanism of the gluconeogenic process. Carbohydrate insufficiency then would be expressed by decreases in concentration of glucose in blood and in concentrations of glycogen and gluconeogenic intermediates within liver that routinely are observed in ketosis (3). Despite the development of a deficiency in glucose supply, it is, nevertheless, possible that glucose entry rate could remain within the normal range during the initial stages of ketosis, before inanition supervened (36).

It can be assumed that the decline in blood glucose concentration, or else some other index of diminished carbohydrate status, would cause a corresponding decrease in blood insulin concentration, which is already low even in healthy lactating cows (already discussed). In support of this assumption, a number of workers have reported that blood concentration and secretory response of insulin are depressed during subclinical ketosis and during development of clinical ketosis (32, 64). That blood acetate concentrations can be elevated during clinical ketosis (41) is also suggestive of a low insulin concentration at this time because acetate utilization appears to be insulin-dependent (35). The low insulin concentration in turn would encourage an intensified mobilization of adipose tissue, thereby releasing increased quantities of NEFA and glycerol, most of which would pass to the liver.

The NEFA can undergo a variety of different fates within liver (Figure 1). Liver becomes infiltrated with fat during ketosis, indicating a significant fraction of assimilated NEFA must be reesterified. Also, a substantial portion of NEFA must be oxidized to ketone bodies. Evidence from other species indicates that the rate of hepatic ketogenesis from NEFA is determined both by rate of supply of NEFA and by carbohydrate status of the liver (74). If the latter is low, as it is in bovine ketosis, then the proportion of assimilated NEFA transformed into ketone bodies will increase.

There has been no exhaustive examination of possible mechanisms whereby carbohydrate sufficiency might determine rate of ketogenesis in bovine liver. However, the finding that oxaloacetate, in common with many other gluconeogenic intermediates, declines in concentration in liver during bovine ketosis has led to the suggestion that ketogenesis might be regulated at the point of entry of acetyl-CoA into the TCA cycle (Figure 1). During ketosis less oxaloacetate would be available for combination with acetyl-CoA, and, hence, more acetyl-CoA would be diverted to ketone body formation (7). One objection to this theory for the regulation of ketogenesis is that it is the intramitochondrial, rather than whole-cell, concentration of oxaloacetate that is likely to be of importance in determining the rate of entry of acetyl-CoA into the TCA cycle because the enzymes of the cycle are located within the

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**Figure 1. Pathways of metabolism of nonesterified fatty acids in the liver.**

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mitochondria. The intramitochondrial concentration of oxaloacetate, which has not yet been determined in bovine liver, need not change necessarily in parallel with the whole-cell concentration. Another possibility, arising from recent work in the rat, is that regulation could occur at the point of entry of NEFA into the mitochondrion (74). According to McGarry and coworkers, the rate of this entry can be determined by the concentration of malonyl-CoA, which inhibits carnitine acyltransferase I (EC 2.3.1.21) (Figure 1). Malonyl-CoA is the product of the acetyl-CoA carboxylase (EC 6.4.1.2) reaction, and in the rat its concentration is proportional both to carbohydrate status and to rate of lipogenesis (46, 48). It is unlikely, however, that malonyl-CoA could be important in the intrahepatic regulation of ketogenesis in the cow, because evidence suggests that the rate of lipogenesis is low in bovine liver (9). An alternative suggestion, based on work in rats, that an increase in carnitine concentration could stimulate hepatic ketogenesis (47) has not received unequivocal support as a regulatory mechanism in ruminants although hepatic concentrations of carnitine and acetylcarnitine increase markedly in fasted ruminants (66). A further possibility, as yet unexplored, is that an intermediate of the gluconeogenic pathway in bovine liver, which is situated at the level of the TCA cycle and whose concentration reflects carbohydrate status, could regulate activity of carnitine acyltransferase II (Figure 1). Finally, it is possible that the low blood concentration of insulin passively increases the rate of hepatic transformation of NEFA into ketone bodies. Although this point has not been investigated in ruminants, studies in nonruminants indicate that insulin exerts an antiketogenic action on liver either by increasing esterification of NEFA or by increasing lipogenesis and, hence, malonyl-CoA concentrations (74). As noted, the second option would not seem to be available to the cow.

Whatever the mechanisms, it must be assumed that during development of bovine ketosis the rate of hepatic ketogenesis is elevated greatly. This rate has not yet been monitored directly in cows suffering from primary ketosis although hepatic ketogenesis is increased in fasting cows (6). Acetoacetate entry rate is substantially increased in sheep suffering from pregnancy toxemia (17). The severity of hyperketonemia produced in bovine ketosis would be increased if there were any limitation to utilization of ketone bodies by peripheral tissues, either as a consequence of the decrease in insulin concentration (32) or a decrease in activity of ketone-body-utilizing enzymes in peripheral organs (71).

Development of ketosis in cows that seem adequately fed but which calve in a fat condition (36) may differ from the account just described. Because the normal environment in early lactation favors mobilization of adipose tissue, one might speculate that in such cows the initial step in the etiology of ketosis is mobilization of an excessive quantity of NEFA and consequent development of a fatty liver. The infiltrated fat then might impair hepatic gluconeogenic capacity. Alternatively, appetite may be depressed in these obese cows so that negative energy balance develops. This in turn would lead to rapid mobilization of fat from the ample stores available.

Relation Between Metabolic Changes and Clinical Signs. Hyperketonemia or hypoglycemia, or both, may lead to loss of appetite and perhaps also appearance of nervous signs. The decline in feed intake then would be expected to lead eventually to the observed decline in milk yield. The loss of body condition would be caused by rapid mobilization of adipose tissue, and also of protein stores, which provide gluconeogenic amino acids to support hepatic glucose production. Remission of ketosis probably occurs because the cow that still is eating eventually will come into approximate energy balance when milk yield has decreased sufficiently.

Source and Nature of Ketone Bodies During Ketosis. On the basis of observations on fasted cows (1, 6), two tentative postulates can be made. The first is that output of ketone bodies from rumen epithelium will not increase during primary ketosis and will tend to decline as food intake diminishes. This decline is because rumen mucosa seems unable to use NEFA as a precursor for ketogenesis in vivo because ketogenesis from this site ceases during fasting when NEFA are the sole available precursor. The second postulate is that when NEFA are the main precursor of ketone bodies, as during both fasting and primary ketosis, the liver will change from producing 3-hydroxybutyrate and
assimilating acetoacetate to producing both these compounds. Consequently, there will be a net output of both 3-hydroxybutyrate and acetoacetate from the splanchnic bed, i.e., gut and liver combined, instead of an output of 3-hydroxybutyrate alone. Acetoacetate, therefore, may be a signal of energy deficiency (61). The suggestion that acetoacetate also plays this role in the rat has been accompanied by demonstration that acetoacetate can decrease glucose uptake by mammary gland (59).

Further Comments on Possible Role of Hormones in Bovine Ketosis. There seems little evidence to corroborate the suggestion of Kronfeld that during development of ketosis the blood concentration of insulin first rises in response to hyperketonemia and then falls once more as hypoglycemia becomes established (36, 37). This hypothesis is based on the theory that rate of glucose supply determines rate of milk output. Whereas it is true that suboptimal milk yield can be raised by increasing glucose supply (40, 43), increase in supply of either glucose or propionate had relatively little effect on milk output in adequately fed animals (25).

Pancreatic glucagon is ketogenic in nonruminants. In addition to stimulating adipose tissue mobilization, it also has a ketogenic effect within the liver that involves increasing rate of passage of NEFA into the mitochondria. This effect may be achieved by decreasing the rate of esterification of NEFA and is mediated via cAMP (74). The behavior of glucagon in bovine ketosis is unknown; but studies with ruminant animals suggest that in these species any ketogenic role of pancreatic glucagon may be muted. For example, in vitro studies indicate that glucagon may be less able to stimulate adipose tissue mobilization in ruminants than in nonruminants (11). While infusion of glucagon does increase hepatic ketogenesis in sheep (19), a major role for the hormone in sustaining ketogenesis is put in question by the observation that administration of somatostatin to alloxan-diabetic sheep fails to alleviate the ketosis, despite a marked decrease in blood glucagon concentration (20). It has been postulated recently by Berzins and Manns (18) that gut glucagon, i.e., glucagon-like immuno-reactivity arising from the intestinal mucosa rather than the pancreas, might play a role in etiology of bovine ketosis because of antagonism to the stimulatory action of pancreatic glucagon on hepatic gluconeogenesis.

A lack of glucocorticoid hormone, from adrenal insufficiency, was at one time thought to be an important factor in development of bovine ketosis (65). Little work has been done in this area in recent years, but as Schultz points out (63), that ketogenic animals respond satisfactorily to adrenocorticotrophic hormone (ACTH) therapy suggests that the adrenal cortex still is functioning adequately. Steroid excretion in the urine is similar in healthy and ketogenic cows (29).

Treatment

The main therapeutic procedures in treatment of bovine ketosis are (63): a) subcutaneous or intravenous administration of substrate quantities of glucose; b) oral administration of propionate or propylene glycol; and c) intramuscular injection of an appropriate glucocorticoid or, alternatively, of ACTH (see above). The rationale behind these procedures is the endeavor to increase the rate of glucose supply (e.g., 63).

Metabolic effects of glucose, propionate, and glucocorticoid have been studied in healthy, fed, lactating cows, and the findings from these experiments permit deductions about the action of the compounds in ketotic cows as well. It seems that the precise therapeutic function of the three compounds may be that of increasing carbohydrate sufficiency by means of increasing glucose supply in the whole animal relative to glucose demand. Increase in carbohydrate sufficiency then is expressed as an increase in blood glucose concentration, and perhaps blood insulin concentration; an increase in hepatic content of glycogen and glucoemic intermediates, particularly at the level of the TCA cycle; and a decrease in hepatic uptake of endogenously-derived lactate and pyruvate (3, 8, 70). The increase in carbohydrate sufficiency is probably then responsible for amelioration of the ketosis, because work in other species indicates that there is an inverse relationship between hepatic carbohydrate status and ketogenesis (74). Glucose, propionate, and glucocorticoids may have different effects on hepatic glucose output, however. Thus, administration of propionate, which is a major glucogenic precursor, will tend to increase hepatic glucose output, but adminis-
tration of glucose will tend to decrease it (8). Whereas glucocorticoid administration may or may not lead initially to a rise in glucose output (38, 57), it seems probable that at 48 h after administration, at least, hepatic glucose output actually is decreased (3, 28).

These conclusions concerning the basis for efficacy of therapeutic compounds receive general support from parallel, but more limited, studies in which glucocorticoid was administered to spontaneously ketotic cows (3), and glucose was administered to cows suffering from fasting ketosis (70).

In recent years evidence has been presented to suggest that nicotinic acid also might be of value in treatment of bovine ketosis. The therapeutic properties of nicotinic acid are said to be from ability of this compound to diminish lipolysis and to increase circulating glucose and insulin concentrations (69, 73).

Prevention

Occurrence of clinical ketosis as a herd problem is usually from faulty nutrition and management and should be minimized by following guidelines for prevention proposed by Schultz (63), Baird et al. (5), and Hibbitt (31). Application of these guidelines apparently has been successful in reducing the incidence of ketosis on selected farms in the UK (31). Adherence to the guidelines also should help to reduce the incidence of severe subclinical ketosis. Clinical ketosis also may occur in only a few cows in a herd. The ketosis in these cows could represent an extreme manifestation of a subclinical ketosis that is pervading the herd as a whole. In this herd situation milk of many cows should give a mild positive reaction to the Rothera test, and the problem may be alleviated by a therapeutic procedure such as administering propylene glycol (26). However, the rest of the herd may be free of ketosis. In this event, it is likely that inherent defects in the affected cows are giving rise to gross glucogenic deficiency. Culling may be the answer in such cases.

SUBCLINICAL KETOSIS

The question arises why all cows that experience negative energy balance in early lactation do not become clinical ketotic. Presumably, this is because most cows are able to tolerate this period without development of any serious discrepancy between glucose demand and glucose supply. Nevertheless, it is probably true that all dairy cows in early lactation show some indication of the same type of metabolic change as that seen in extreme form in cows suffering from ketosis (2, 70). Biochemical changes in clinically ketotic cows simply represent one end of a continuous spectrum of possible responses to negative energy balance, to the metabolic priority enjoyed by milk production, and to the propensity for fat mobilization in early lactation. It follows that in early lactation there are likely to be many dairy cows in which marked indications of carbohydrate insufficiency and fat mobilization can be detected, but which do not exhibit any clinical signs of ketosis. When these indications include hyperketonemia and hypoglycemia, the cows may, in accordance with common practice in the literature (26, 27, 55, 64), be considered to be suffering from subclinical ketosis. In such cows the whole-blood concentration of total ketone bodies normally does not exceed 1.5 to 2.0 mM. The importance of subclinical ketosis is that the condition may remain undetected and, hence, untreated, and yet have adverse effects on productivity which parallel those elicited by clinical ketosis.

KETOSIS AND THE IMPAIRMENT OF PRODUCTIVITY

Marked carbohydrate insufficiency and fat mobilization, as in ketosis, may adversely affect productivity of cows above and beyond reduction in milk yield. That is not surprising considering the implications of biochemical and ultrastructural changes that can occur. For example, many peripheral organs may be less able to assimilate glucose, acetate, and ketone bodies from the blood because uptake of these compounds is mediated by insulin, the concentration of which decreases (32, 35, 64). That lactation itself, regardless of the development of clinical or subclinical ketosis, leads to some decrease in the ability of peripheral organs to extract energy from glucose, is suggested by the observation that conversion of glucose to carbon dioxide decreases with onset of lactation (10, 15).

Some impairment of liver function also would be expected. As has been noted already, in clinical ketosis the liver becomes infiltrated.
with fat and loses glycogen and glucogenic intermediates. It also loses NAD$^+$ (3). Similar, but less marked, changes also would be expected in subclinical ketosis. Ultrastructural studies have not been performed on livers of spontaneously ketotic cows. However, there is a loss of rough endoplasmic reticulum and a decrease in mitochondrial number in fatty liver in lactating cows suffering from fasting ketosis (56), and it seems entirely possible that similar ultrastructural changes could occur when ketosis arises spontaneously. One indication of impairment of liver function is provided by the observation that bromosulphthalein is cleared more slowly during ketosis (58). It also seems reasonable that oxidative and synthetic functions could be diminished.

One important way in which ketosis adversely may affect productivity is by decreasing fertility. Several authors have observed that either high milk production or low energy intake can lead to impairment of reproductive function in dairy cows (42, 51, 68). This suggests that diminished fertility may be one consequence of exposure to subclinical ketosis, because both high milk output and energy deficiency likely are associated with marked indications of lipid mobilization and carbohydrate insufficiency. According to some authors the feature of prime importance in disrupting reproductive function is low blood glucose concentration and consequent decline in uptake and metabolism of glucose by peripheral organs (45, 52). However, there is also evidence of a correlation between elevated blood ketone body concentration and diminished fertility, suggesting that lipid mobilization could be involved (14, 26).

There have been several reports of a correlation on a herd basis between incidence of clinical ketosis and incidence of infertility (54, 55, 62). These reports are of interest because the ketosis normally would have been treated, and the cows apparently recovered before the time for insemination arrived. Therefore, there are two possibilities. First, exposure to clinical ketosis may have had long effects on reproductive potential even after signs of ketosis had subsided. Second, some degree of subclinical ketosis may have persisted up to the time of insemination. This second possibility seems to be more likely, because in another experiment cows that had shown ketosis but had been put out to grass before insemination, showed no diminution in fertility (50). It is probable that any subclinical ketosis would have disappeared completely in these cows at insemination. The importance of glucose status at insemination is emphasized by the observation that conception occurs in beef cows when blood glucose concentration is rising but not when it is falling (21).

Sommer (67) has developed the interesting concept that impaired liver function could be a salient feature of what he terms a "parturition syndrome" in dairy cows. According to his theory, the parturition syndrome is a complex of pathological changes in organ function and structure that occur in the cow in response to metabolic stress imposed during the period from late gestation through to next conception. The various disorders during this period are then signs of the syndrome and include not only metabolic disorders and diminished fertility but also infectious diseases such as mastitis. In the latter case the suggestion is that organ or cellular malfunction renders the animal less able to resist infection. Sommer's far-reaching concept requires corroboration. Baumgartner (13) recently questioned the claim by Sommer that periparturient abnormality may be predicted from blood metabolite concentrations in late pregnancy.

OUTLOOK

According to Hibbitt (31), average milk yield of individual dairy cows has increased by some 25% over the past 20 yr. There appear to be two major possibilities for the future. One is that the present trend of attempting to increase milk output per cow will continue. The other is that there will be a trend toward achieving substantial milk yields when animals are fed poor quality materials, such as animal waste, that are of no value in human nutrition. In either case, it seems likely that ketosis will remain an important impediment to productivity because in the first instance output is being increased and in the second input diminished. In both cases, therefore, there will be a tendency for the balance between glucose supply and glucose demand to be jeopardized.

For the present, however, it seems that clinical ketosis can be contained more or less by good management. In the immediate future,
therefore, it seems most valuable to attempt to achieve a proper appreciation of the impact on productivity of subclinical ketosis, as defined in this review. More information is required about the incidence of this subclinical condition. More exhaustive and definitive information also is required on the extent to which appearance of signs of subclinical ketosis can be correlated with impaired productivity. Because features of subclinical ketosis mainly arise in response to negative energy balance, it would be worthwhile considering whether this negative energy balance must be accepted as an inevitable feature of early lactation in high-producing cows or whether the magnitude of the energy deficit could not be decreased in some way. Such a decrease might be achieved, for example, by increasing energy content of feed. One possibility is that of using protected tallow, which might have a glucose-sparing effect (39, 53). The supply of fat simultaneously would be increased, however, thus increasing the risk of hyperketonemia.

At a more fundamental level it would be of great value to identify biochemical mechanisms by which energy deficiency adversely can affect productivity. Furthermore, to understand and thereby possibly to regulate development of negative energy balance, it would be necessary to achieve better insight into such areas as assignment of metabolic priority to milk production, effect of milk production on intermediary metabolism, control of appetite, and interaction between feed intake and intermediary metabolism. In all these areas, hormones play a vital part. Study of endocrine controls of intermediary metabolism in the ruminant, however, is still in its infancy. This is a fertile field for research.

REFERENCES


