SUMMARY

Laminitis often follows lactic acidosis and is accompanied by increased blood and rumen histamine. However, since histamine is poorly absorbed and absorbed histamine is rapidly metabolized, and since high levels of oral histamine have not produced laminitis, it is unlikely that ruminal histamine causes laminitis.

Lactic acidosis leads to rumenitis, which, in turn, leads to liver abscesses because the causative microorganism can now cross the rumen wall into portal circulation. In cattle, hair ingested during grooming may penetrate the rumen wall and aid in this passage. Immunizing cattle against liver abscesses may be possible.

Polioencephalomalacia occurs because an enzyme, thiaminase, develops in the rumen, catalyzing the production of a thiamin antagonist. Lactic acidosis may set up ruminal conditions that encourage this chain of events.

(Key Words: Acidosis, Laminitis, Histamine, Rumenitis, Liver Abscesses.)

INTRODUCTION

Rumen acidosis leads to a number of direct and indirect metabolic consequences, any of which can, in turn, lead to other ailments. Lactic acid accumulates and pH decreases in the rumen and blood. Ruminal osmotic pressure increases ruminal water uptake and causes hemoconcentration and disturbances in electrolyte balance. All these physiological consequences of lactic acidosis might, in turn, produce a wide range of other problems, including directly irritating gastrointestinal epithelium and initiating profound changes in the microbial rumen population. While a wide range of feedlot ailments might be secondarily implicated, this paper deals mainly with laminitis, the rumenitis-liver abscess complex, and polioencephalomalacia.

LAMINITIS

The histopathology of bovine laminitis has been described by Maclean (1966, 1971) and by Nilsson (1963). They recognized an acute form, characterized by hyperemia, hemorrhage, and thrombosis with edema in surrounding tissues, and a chronic form with similar but more severe vascular changes and laminae compressed by extensive fibrous tissue formation in the cornium. The pathological changes suggest stagnant hypoxia.

Bovine laminitis, being generally associated with high concentrate intakes, has led to its presumptive relationship to lactic acidosis. Dirksen (1969) observed hoof sloughing in the succeeding months after lactic acidosis; Maclean (1969) estimated a 1 to 9% incidence of laminitis in “barley beef” units in Great Britain. However, Jubb and Kennedy (1970) noted that laminitis is also associated with other conditions (especially in horses) including purging, metritis (particularly with retained placenta), ingesting cold water after strenuous exercise, and prolonged standing.

Because histamine is found in the rumen fluid of lactic acidotic animals (Dain et al., 1955), because the histopathology of laminitis resembles the circulatory effects of histamine (capillary permeability and arteriolar dilation), and because good clinical results may be obtained with antihistamines given in early laminitis (Jubb and Kennedy, 1970) histamine is often considered responsible for laminitis (Dirksen, 1969). Serum histamine is slightly elevated during acute laminitis of cattle on high concentrate rations, but is higher if laminitis progresses to the chronic stage (Maclean, 1970).
But does the blood histamine come from the rumen or from somewhere else, with rumen histamine being only coincidental? Several lines of evidence point to the latter view, and this is supported by Maclean (1970).

Histamine absorbed into portal circulation is rapidly metabolized to inactive forms by either methylation or oxidation (Goth, 1974). Care must be taken to exclude these metabolically inactive forms from histamine analysis. The fluorometric orthopthaldehyde method (Shore et al., 1959) excludes those metabolites. Histamine is a highly dissociated acid, and rapid histamine absorption seems unlikely. Wrenn et al. (1964) found more urinary histamine excreted from cattle fed corn silage (high in histamine) than cattle fed grass silage or hay, indicating at least some absorption. But these animals were not acidotic.

Serum histamine is more likely to come from the laminitic tissue. Mast cells store histamine in granules, and then degranulate, releasing histamine during tissue injury (Bloom and Fawcett, 1968). Other causes for mast cell degranulation and histamine release include surfactants (compound 48/80, a polyamine has been used as an experimental model), antigen-antibody reactions and some drugs (Goth, 1974). When rumen bacteria lyse at low pH, it seems logical that the resulting endotoxin release might, in turn, release histamine.

While lactic acidosis and laminitis appear to be statistically related, the biochemical relationships remain obscure. Laminitis probably is not caused by ruminal histamine. Certainly, not all laminitis is related to acidosis. Merritt and Riser (1968) described a laminitis in Jersey cattle of possible hereditary origin. Maclean (1968) described acute laminitis in the sow. Still, feedlot laminitis is largely associated with lactic acidosis. Maclean (1966) discussed the possibility of laminitis arising from allergic reactions, a hypothesis which now seems logical.

**Rumenitis and Liver Abscesses**

When high concentrate feeding became common, condemned livers due to abscesses increased dramatically. In the year ending June, 1973, about 10.8% of cattle slaughtered in the United States had abscessed livers (Federal Meat and Poultry Inspection, 1974)—a serious dollar loss, especially since the incidence in a particular group may be as high as 95% (Jensen and Mackey, 1971). Also, healed scars from old abscesses may result in condemnation or trimming.

Rumenitis and liver abscesses appear inseparable as ruminitis (a consequence of acidosis) probably allows microorganisms to enter portal circulation. That hypothesis is supported by the following: (1) Most liver abscesses contain *Spherothorax necrophorus* (also known as *Fusiformis necrophorus*) (Newsom, 1938; Madin, 1949); (2) *Spherothorax necrophorus* is in the rumen and feces of most healthy and diseased cattle (Robinson, et al., 1951); and (3) *Spherothorax necrophorus* injected into the portal vein produces liver abscesses (Jensen et al., 1954).

Wieser et al. (1966) found no relationship between rumen and liver lesions. However, only a small break in rumen epithelium integrity would permit bacterial entry into the portal circulation. Secondly, freedom from rumenitis at slaughter may be a poor indicator of the situation early in the feeding period. An early rapid change in concentrate may have induced lactic acidosis, causing subsequent rumenitis and allowing liver abscess initiation after which the abscesses developed but the rumenitis healed.

Jensen et al. (1947) found that telangiectasis, also known as "telang liver" predisposes to liver abscesses. Andersen (1955) noted that telangiectasis is due to erosion of liver parenchyma, not to liver necrosis. "Telang" and "sawdust liver," a precursor of telangiectasis, were the most common reasons for condemning livers, following abscesses and liver parasites (Federal Meat and Poultry Inspection, 1974).

As rumenitis and hyperkeratosis appear to predispose to liver abscesses, understanding why rumenitis develops is essential. Possible reasons include high organic acid (lactic) concentrations, the resulting low pH and high
osmotic pressure, bacterial endotoxins, and the fact that any one or any combination of these factors may render the epithelium susceptible to mechanical injury. In an experiment with young calves fed barley (Kay et al., 1969), rumen pH averaged 5.55 in controls, 5.85 in those on barley with 7.5% sodium acetate, and 6.18 in those on barley with 7.5% sodium bicarbonate. At slaughter, controls had developed rumenitis but the bicarbonate-fed animals had practically none. Sodium acetate produced intermediate results. This indicates that pH may have been more critical than acid concentration. Although those authors made extensive observations on the rumen epithelium, they mentioned no liver abscesses.

Fell et al. (1972) have taken an intriguing approach to the rumenitis problem. They noted that rumens of sheep on high concentrate diets underwent hypertrophic and hyperplastic changes but none of the inflammatory changes seen in cattle on similar diets. When cattle were covered with canvas coats, and any exposed areas clipped, their rumens were similar to those of sheep, even though barley perling residue (containing siliceous plant spicules) was added to their diets. Adding 2 g clipped cattle hair per day to the sheep diets produced rumen wall edema, granulation, fibrin exudation, and abscesses, all typical of rumenitis. They concluded that plant spicules cause little damage in rumens and that one of the causes of rumenitis is hair ingested while licking and grooming. Although none of their animals had liver abscesses, photomicrographs showed short pieces of hair embedded in ruminal folds and through the epithelium, suggesting a route for bacteria to enter portal circulation. While sheep rumens contained wool, its crimped nature apparently prevented its penetrating the rumen epithelium.

Salivary buffering (largely bicarbonate) must be considered in lactic acidosis from the standpoint of both instantaneous pH and its ability to resist pH change. Church (1969) reviewed saliva production and function and cited data by Bailey (1959) showing .68 g saliva produced per gram of pelleted ration, and 3.63 g produced per gram of long hay. Saliva productions per unit of ruminating time were similar irrespective of ration fed. Balch (1971) proposed using chewing time (sum of eating and ruminating, expressed as minutes per kilogram dry matter) as a "roughage value index" (RVI). As saliva produced per unit chewing time is nearly constant, RVI should indicate the ability of a roughage to stimulate saliva secretion and, thus, buffer the rumen. Because fine grinding or pelleting roughage may decrease chewing time and salivary output (Bailey, 1959), rations must be evaluated on their physical characteristics as well as their roughage-to-concentrate ratios. When Utley et al. (1973) fed steers 80% concentrate and 20% whole peanut hulls, only 3.7% had liver abscesses, but 56% had abscesses when hulls were ground and 59% when they were pelleted.

A system has been developed by Law and Sudweeks (1975) to monitor time spent chewing, and Sudweeks et al. (1975) have used the instrument to measure chewing times of steers on several rations. Using several roughage:concentrate combinations, and partitioning chewing time due to roughage and concentrate by regression analysis, they found RVI's as follows: wheat silage, 68.9 ± 3.2 SE; corn silage, 67.3 ± 1.2; sorghum silage, 59.7 ± 2.4; bermudagrass hay, 78.5 ± 5.5; citrus pulp, 30.9 ± 15.2; ground corn, 5.1 ± 4.2; and soybean mill feed, 8.4 ± 2.8.

A wide range of products, including paper, rice hulls, cottonseed hulls oyster shells, corn cobs, plastic, sand, and sawdust have been used as roughage substitutes (Slyter and Kamstra, 1974). Because of the paramount importance of salivary buffering to acidosis, rumenitis, and subsequent liver abscesses, such products should be evaluated according to RVI. If high concentrate diets must be fed, the best current answer to liver abscesses seems to be low level antibiotic feeding. Jukes (1971) cited much of the background work.

A new approach with considerable possibility is that of Garcia et al. (1974) who have successfully immunized cattle against liver abscesses using Spheroborus necrophorus toxoid.

POLIOENCEPHALOMALACIA

Jubb and Kennedy (1970) have described the pathology of polioencephalomalacia (PEM). Signs include dullness and sometimes blindness, progressing to muscular tremors (especially of the head), and opisthotonos. Animals tend to press on fixed objects with their heads. They progress to convulsions with persistent opisthotonos and nystagmus, and may die after one to several days in a coma. Survivors may be blind, and at least partially decorticate. Gross pathology includes brain swelling, with flattened gyri.
If the animals survive several days, the brain may be displaced caudally with herniation of the medulla and cerebellum into the foramen magnum. The dorsum of the hemispheres loses the normal brain turgidity and softens. The surfaces of the gyri become yellowish brown. Histologically, the necrosis is laminar, with neurons shrunken, acidophilic, and surrounded by clear space.

The condition was first described in the United States by Jensen et al. (1956) in Colorado and neighboring states. It has been reported since then in many locations. In British literature, it is called cerebrocortical necrosis (CCN).

PEM was attributed to a wide variety of causes (Jensen and Mackey, 1971), but was finally shown to respond to large, intravenous doses of thiamin (Davies et al., 1965). The thiamin status of ruminants is generally considered adequate even though rumen synthesis may be low (Hungate, 1966). However, PEM often occurs on high-concentrate diets, where exogenous thiamin should be high. The signs must be caused by a reversible biochemical defect, since recovery is rapid when thiamin is given soon enough. So cells might be thiamin deficient; or a thiamin antimetabolite might be blocking thiamin dependent reactions. We have examined those possibilities, as have workers in Great Britain and Canada.

Edwin et al. (1968a) proposed that PEM might be caused by an enzyme, thiaminase, and later (Edwin et al., 1966b) demonstrated thiaminase in the rumen fluid of PEM (CCN) animals.

PEM research was difficult because only spontaneous cases were available and then usable only a limited time. At Kansas State University, Parks (1970) and Lusby (1971) hyperalimented lambs using continuous intraruminal infusions of a highly fermentable diet. The lambs died after a maximum of 21 days (Parks et al., 1971). Cause of death was later found to be PEM (Lusby and Brent, 1972), with ruminal thiaminase (Sapienza and Brent, 1972). With high energy levels, the model could produce PEM in as little as 4 days.

Dixon and Webb (1964) differentiate two types of thiaminase. Thiaminase I (E.C.2.5.1.2) substitutes a new nitrogenous base for the thiazole moiety of thiamin, while thiaminase II (E.C.3.5.99.2) splits the thiamin at the methylene bridge. Thiaminase II would only decrease the amount of thiamin available for absorption, but thiaminase I could create thiamin analogs capable of acting as thiamin antimetabolites.

Edwin and Jackman (1970) proposed the thiaminase in PEM (CCN) was thiaminase I. Data from Lusby and Brent (1972) support the thiaminase I hypothesis because it is unlikely that simple thiamin deficiency could develop in 4 days even if no thiamin were absorbed.

Since thiaminase I carries out a base exchange involving the thiazole ring, a co-substrate is essential. Fujita et al. (1952) studied a wide range of co-substrates with thiaminase I from shell-fish, fresh water fish, and bacteria (Bacillus thiaminolyticus). Several nitrogen-containing bases were quite active, including both nicotinic acid and nicotinamide. The pH optimum for bacterial thiaminase I was 5.0.

Morgan and Lawson (1974) isolated from the rumens and feces of PEM sheep, thiaminase I-producing bacilli that were weakly gram-positive and formed rods after 48 hours. Pyrimidinyl-nicotinic acid was isolated as a reaction end-product, indicating that a base-exchange reaction had occurred. Thiaminase I-producing Clostridium sporogenes has been isolated from CCN animals by Shreeve and Edwin (1974).

Lactic acidosis appears to establish rumen conditions conducive to PEM development. As lactic acidosis develops, the rumen population changes from predominately gram-negative species to predominately gram-positive with an increase in bacilli. The pH drops to near optimum for bacterial thiaminase I, and histamine accumulates. Fujita et al. (1952) found that compounds similar to histamine were potent thiaminase I co-substrates.

Considering the wide variety of bases available in the rumen, several thiamin analogs are possible. Histamine should give rise to an imidazole thiamin analog. Nicotinic acid thiamin analogs have been isolated from rumen fluid (Edwin and Jackman, 1970). Compounds exhibiting different extraction characteristics and fluorescence spectra from those of thiochrome have been found during thiamin analysis of rumen fluid containing thiaminase (D. A. Sapienza, unpublished data).

The known thiamin antimetabolites vary in biochemical and physical modes of action. For example, Amprolium, a potent coccidiostat and thiamin analog, is incapable of being phosphorylated, and when fed at extreme levels (1.5% of the diet) can produce PEM (Lowe and Dunlop, 1972; Markson et al., 1974). Pyrithiamin can inhibit both thiamin phosphorylation
reactions and reactions requiring thiamin pyrophosphate. Oxythiamin blocks reactions as does pyrithiamin, but oxythiamin does not appear to interfere with the nervous system. Thiamin antagonysts have been reviewed by Rogers (1962). Unphosphorylated thiamin may have a specific role in ion transport in nerve tissue, independent of its coenzyme role (Cooper et al., 1969), so thiamin’s absence, or the presence of an analog might cause a wide variety of nerve symptoms. Considering the diverse activity of thiamin and its analogs, the wide range of signs seen in PEM is not surprising.

Animals changed very rapidly to high concentration rations develop ruminal thiaminase (Sapienza and Brent, 1974). Although lactic acidosis may occur before thiaminase develops, in our studies thiaminase did not develop without acidosis. Many questions on the relationship between lactic acidosis and thiaminase remain unanswered. For example, is acidosis a cause or an effect of thiaminase activity? Both make metabolic sense. Pyruvate decarboxylase requires thiamin pyrophosphate (TPP). Absence of TPP or the presence of a TPP antimetabolite either here, or in the citric acid cycle could cause pyruvate, and, subsequently, lactate accumulation. Is thiaminase I always in the rumen, only requiring the co-substrate to become active? If thiaminase I is the culprit in PEM, then what metabolic analogs are produced and what bases are involved? If nicotinic acid is a co-substrate for thiaminase I, is a deficiency of nicotinic acid a possible consequence of PEM? Finally, what causes thiaminase to become active in the rumen, and what can be done to inhibit its activity or prevent it from developing?

LITERATURE CITED


