Relationship of Fat Metabolism to Health and Performance in Dairy Cattle

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The incidence of fat-mobilization associated disorders in dairy cows.

Adipose mobilization with an increase in circulating nonesterified fatty acids is a usual and predictable effect occurring in response to impending parturition and the initiation of lactation in dairy cows (Metz and van den Bergh 1977). Associated with adipose mobilization is an increase in serum ketone body and hepatic triacylglycerol (TG) concentrations, each of which may have adverse effects on health and productivity. Elevation in hepatic TG concentration is manifest as fatty liver (FL), which appears to be extremely common. The probable frequency with which FL occurs in the dairy cattle population may be appreciated from the data of Jasper (1947) as shown in the table below. Various and more quantitative studies have been carried out on smaller populations since that time (Reid 1980, Gerloff *et al.* 1986, Smith 1987, van Dijk *et al.* 1989). All have indicated that fatty liver of some degree is found in a large portion probably the majority, of peripartum dairy cows.

TABLE - Incidence of fatty liver, as determined by visual evaluation of liver color, in a large group of slaughtered dairy cows (Jasper 1947)

Reproductive stage	Number of animals	Percent fatty liver	Percent questionable fatty liver
Not peripartum	2309	0.87	3.2
Advanced gestation	60	40.0	18.4
Recent parturition	25	24.0	8.0

The effects of fatty liver on disease risk and immune function

Disease risk appears to increase linearly with liver fat concentration and is usually significantly elevated in cows with greater than 10% liver TG (Gerloff *et al.* 1986, van Dijk *et al.* 1989). Recent research at Colorado (Curtis 1989) has suggested that there may be a curvilinear increase in the risk of clinical mastitis as liver fat content goes from 5% to 60% (volumetric[1]). Futhermore, on a clinical basis, low leukocyte counts are commonly associated with severe FL. Thus, it appears that FL is associated with immunosuppression but the mechanism(s) for this effect are not clearly established.

There is evidence (Kehrli *et al.* 1989ab) suggesting that both the phagocytic and lymphocytic arms of the cellular immune system are suppressed in postpartum cows, but whether or not this is associated with FL has apparently not been investigated. More specifically related to lipid metabolism and FL are reports that ketone bodies and hyperketonemia may be immunosuppressive in cattle (Targowski and Klucinski, 1983, Targowski *et al.* 1985). Given that hyperketonemia and FL appear to be part of the same syndrome of intense fat mobilization, it could be that hyperketonemia is, at least in part, a mechanism for the reduced resistance to infectious diseases observed with FL.

Another means by which the immune system could be affected by FL is through serum lipoproteins. It appears clear that fatty liver in cows is associated with a fall in serum lipoprotein concentrations, especially lipoproteins of the low and very-low density classes (Herdt *et al.* 1983, Rayssiguier *et al.* 1988, Garry *et al.* 1989). Emerging evidence suggests a role for serum lipoproteins in modulation of the immune system (Edgington and Curtiss 1981; Cuthbert and Lipsky 1987; Jurgens *et al.* 1989). However, the exact nature of the immunomodulating effect of serum lipoproteins is as yet unknown, with some reports suggesting an immunostimulatory effect and others an immunosuppressive action.

Finally, immunosuppression in FL may simply be a reflection of the negative energy balance that accompanies FL. Immunity appears to be the physiological function most sensitive to undernutrition (Chandra, 1983). Thus, the calorie or protein/calorie deficts of late gestation and early lactation, which may be exacerbated by FL, may be the cause of at least a portion of the apparent immunosuppression.

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[1]Liver fat concentrations are variously reported on either a volumetric or gravimetric basis; volumetric values in percent appear to be approximately twice as high as gravimetric values determined on the same tissue (Gaal et al. 1983).

Fatty liver and dry matter intake

Dry matter intake is an important variable in dairy cows, especially during the early weeks of lactation in which appetite remains paradoxically low while rising milk yield causes rapid increases in energy demand. While no definitive evidence exists, several observations suggest that appetite may be depressed by FL. These observations include the pattern of decline in feed intake pre- and postpartum. This pattern, as noted by Zamet and co-workers (1979ab), coincides with the pattern observed for fat accumulation and subsequent disappearance from the liver (Husveth *et al.* 1982), thus there is a temporal association suggesting a relationship between FL and appetite reduction. Futhermore, the degree of reduction in appetite prepartum is related to disease risk postpartum (Zamet *et al.* 1979a, Zamet *et al.* 1979b) again suggesting a relationship between FL and feed intake. In other observations, it appears that body condition at calving has an important influence on postpartum appetite, with fatter cows having poorer appetites (Garnsworthy and Topps, 1981). The association of FL with adipose mass and body weight loss appears to provide a possible explanation for these differences in appetite between thin and fat cows. Also suggesting a role for FL in appetite suppression is the clinical observation that anorexia is often one of the first signs of extreme FL in cows.

While the above observations suggest a role for FL in determining dry matter intake in dairy cows, this relationship does not appear to have been examined directly. There is, however, a large body of evidence in small monogastrics indicating that the liver plays a direct role in appetite regulation (Scharrer and Langhans 1988, York 1990). Specifically, it appears that low intrahepatic NAD-/NADH ratios, such as occur during fatty acid oxidation, stimulate vagal afferent fibers that in turn suppress appetite centers in the brain. A suppressive role for FL in appetite control is a particularly interesting possibility because, if present, it could lead to a vicious cycle in which reduced feed intake leads to increased adipose mobilization which would, in turn, lead to continued elevation in liver fat with further suppression in feed intake (figure 1). Breaking this cycle would then provide the key to preventing severe fatty liver.

Fatty liver and reproductive efficiency

An apparent relationship exists between the severity of fatty liver and reproductive efficiency, as measured in days until conception (Reid 1983, Reid *et al.* 1983, Gerloff *et al.* 1986, van Dijk *et al.* 1989), however, the mechanism of this effect is unknown. Poor reproductive performance could be directly related to FL, or the two may merely be associated by a relationship to a third factor, such as negative energy balance (figure 2). Negative energy balance is

Figure 1 Potential feed back loop illustrating the way in which fatty liver may be self perpetuating

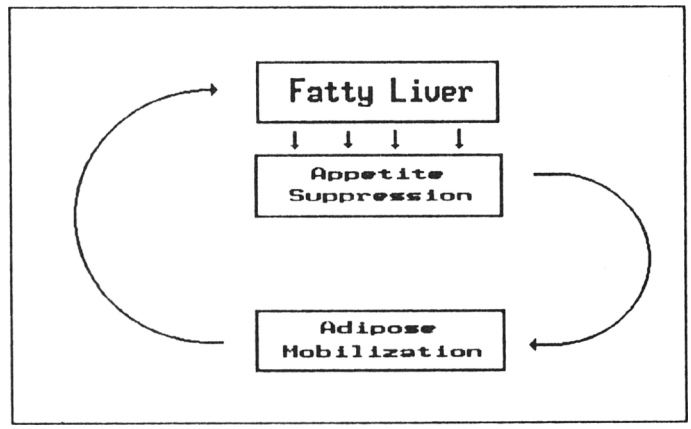
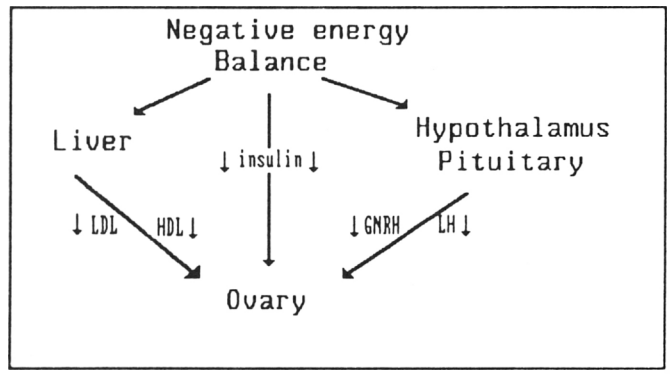


Figure 2 There are several ways in which negative energy balance may have an adverse impact on ovarian function



necessary for the development of FL and also is known to suppress reproductive activity. Elaborate hypotheses have recently been presented describing ways by which fertility may be impaired by the influence of negative energy balance acting the hypothalamic, pituitary and ovarian level (Butler and Smith, 1989), without the necessity of any hepatic involvement. However, there is at least one mechanism by which FL may potentially influence ovarian function directly and that is via reduced delivery of cholesterol to the ovary for progesterone synthesis.

A source of preformed, extracellular cholesterol is required for maximum synthesis and secretion of progesterone (Pate and Condon 1982, O'Shaugnessy and Wathes 1985). In the body, cholesterol is delivered to endocrine tissues, including the ovary, by serum lipoproteins that are synthesized in either the liver or small intestine. The lipoproteins involved with cholesterol transport are the low-density lipoproteins (LDL) and high-density lipoproteins (HDL), and serum concentrations of both LDL and HDL are decreased in FL (Herdt *et al.* 1983, Rayssiguier 1988, Garry *et al.* 1987).

The dominant lipoprotein delivering cholesterol to

the ovary may change during the estrus cycle. Early in the cycle, progesterone synthesis begins in the granulosa cells of the follicle. Synthesis continues after ovulation as the granulosa cells transform into the luteal cells of the corpus luteum. In the follicular phase, lipoproteins may only reach the granulosa cells after diffusion across the basement membrane of the follicle. This membrane presents a formidable barrier; no LDL reaches the follicular fluid and follicular HDL concentrations are considerably below plasma concentrations (Brantmeier *et al.* 1987, Savion *et al.* 1982). Due to the basement membrane diffusion barrier, the FL associated fall in serum HDL may lead to a severe reduction in follicular HDL. The influence of HDL delivery to granulosa cells may be particularly important because progesterone production by the follicle appears to be an important part of the follicular maturation process and may affect ovulation and the function of the subsequent corpus luteum (McNatty and Sawers 1975, McNatty *et al.* 1975).

In contrast to the limited availability of serum lipoproteins to the granulosa cells, the profuse vasculature and highly fenestrated endothelium of the corpus luteum allows the luteal cells nearly unlimited access to serum lipoproteins, including LDL. This is in contrast to most tissues in which access to plasma LDL is limited due to the poor perfusion of LDL through the endothelium of unfenestrated capillaries. Luteal cell membranes have high concentrations of LDL receptors and it appears that LDL is the perdominant supplier of cholesterol for progesterone synthesis by these cells. The fall in serum LDL associated with FL may affect luteal progesterone synthesis, however the vascular arrangement may make luteal cells more resistant than granulosa cells to changes in serum lipoprotein concentrations.

Although the evidence supporting a direct role for hypocholesterolemia as a cause for ovarian dysfunction and infertility in dairy cows is primarily speculative, there is considerable empirical evidence supporting this relationship. The report of Williams (1989) is perhaps the most definitive data available to indicate a direct relationship between serum lipoproteins and ovarian function. In this study, *Bos indicus* cows were divided into two groups, one of which was fed supplemental fat as whole cotton seeds while the other was fed a diet containing no supplemental fat. Three weeks postpartum all cows had their calves temporarily removed and were given gonadotropin releasing hormone to induce ovulation. Progesterone production was monitored throughout the life span of the ensuing corpus luteum. Cows receiving supplemental fat were observed to have higher serum cholesterol and higher serum progesterone, compared to the cows not receiving supplemental fat. In addition, there was a difference in the life spans of the corpora lutea which were maintained for the normal period of approximately 15 days in the fat-fed cows but regressed after 7-8 days, on average, in the control cows. These data are particularly interesting because the diets were formulated to be isocaloric, indicating that the observed experimental differences were not due to differences in energy balance.

In conclusion, there are numerous ways in which fat metabolism, especially adipose lipolysis, may influence animal health and performance. Hyperketonemia and FL appear to be important responses to adipose mobilization that may directly or indirectly influence health and performance. In the case of FL, it should be appreciated that most of the potential relationships to health and production are not related to liver functions classically evaluated in clinical laboratories. Therefore, as we continue to study FL it will be important to monitor metabolic activities of the liver that may be specifically involved with immunity, appetite, reproductive or other functions that could subtly interact with health and production.

Summary

Rapid mobilization of adipose fat accompanied by hyperketonemia and fatty liver (FL) is extremely common in peripartum dairy cows. Previous reports indicate an inverse relationship between liver fat concentration and disease resistance. Such a relationship could be mediated through a hyperketonemic suppression of cellular immunity, altered serum lipoprotein concentrations or other effects associated with negative energy balance. Appetite reduction may be associated with fat mobilization and this could be due to FL and the direct effects of the liver on food-intake centers of the brain. Reproductive efficiency is reduced in association with FL; such an association could be due to FL-associated hypolipoproteinemia and the need for serum lipoproteins to support maximal progesterone synthesis by the ovary.

References

Brantmeier, S. A., Grummer, R. R., Ax. R. L. (1987): Concentrations of high density lipoproteins vary among follicular sizes in the bovine. J. Dairy Sci. 70,2145. Butler, W. R., Smith, R. D. (1989): Interrelationships between energy balance and postpartum reproductive function in dairy cattle. J. Dairy Sci. 72,767. Chandra, R. K. (1983): Nutrition and immune responses. Can. J. Physiol. Pharm. 61,290. Curtis, C. R. (1989): The marriage of epidemiologic and experimental research: A unified approach. Proceedings, 7th International Conference of Production Disease in Farm Animals, pp74. Cuthbert, J. A., Lipsky, P. E. (1987): Provision of cholesterol to lymphocytes by high density and low density lipoproteins. Requirement for low density lipoproteins receptors. J. Biol. Chem. 262,7808. Edgington, T. S., Curtiss, L. K. (1981): Plasma lipoproteins with bioregulatory properties including the capacity to regulate lymphocyte function and the immune response. Cancer Res. 41,3786. Gaal, T., Reid, I. M., Collins, R. A., Roberts, C. J., Pike, B. V. (1983): Comparison of biochemical and histological methods of estimating fat content of liver of dairy cows. Res. Vet. Sci. 34,254. Garnsworthy, C., Topps, J. H. (1981): Food intake by dairy cows in relation to body condition at calving and subsequent performance. Anim. Prod. 32,392(abst). Garry, F. B., Curtis, C. R., Ford, R. B., Smith, J. A. (1989): Changes in liver fat infiltra-

tion, serum lipid concentrations and body condition scores in dairy cattle. Proceedings, 7th International Conference on Production Disease in Farm Animals, pp285. Gerloff, B. J., Herdt, T. H., Emery, R. S. (1986): The relationship of hepatic lipidosis to health and performance in dairy cattle. J. Am. Vet. Med. Assoc. 188,845. Herdt, T. H., Liesman, J. S., Gerloff, B. J., Emery, R. S. (1983): Reduction of serum triacylglycerol-rich lipoprotein concentrations in cows with hepatic lipidosis. Am. J. Vet. Res. 44,293. Husveth, F., Gaal, T. (1982): Peripartal fluctuations of plasma and hepatic lipid components in dairy cows. Acta Vet. Sci. Hung. 30,97. Jasper, D. E. (1947): Hepatic changes in the bovine during pregnancy and ketosis. PhD thesis, University of Minnesota, Jurgens, G., Xu Q. B., Huber, L. A., Block, G., Howanietz, H., Wick, G., Traill, K. N. (1989): Promoting o lymphocyte growth by high density lipoprotens (HDL). Physiological significance of the HDL binding site. J. Biol. Chem. 264,8549. Kehrli, Jr. M. E., Nonnecke, B. J., Roth, J. A. (1989a): Alterations in bovine neutrophil function during the periparturient period. A. J. Vet. Res. 50,207. Kehrli, Jr. M. E., Nonnecke, B. J., Roth, J. A. (1998b): Alterations in bovine lymphocyte function during the periparturient period. Am. J. Vet. Res. 50,215. McNatty, K. P., Sawers, R. S. (1975): Relationship between the endocrine environment within the graafian follicle and the subsequent rate of progesterone secretion by human granulosa cells *in vitro*. J. Endocr. 66,391 Metz, S. H. M., van den Bergh, S. G. (1977): Regulation of fat mobilization in adipose tissue of dairy cows in the period around parturition. Neth. J. Agric. Sci. 25,198. O'Shaugnessy, P. J., Wathes, D. C. (1985): Role of lipoproteins and de-novo cholesterol synthesis in progesterone production by cultured bovine luteal cells. J. Reprod. Fert. 74,425. Pate, J. L., Condon, W. A. (1982): Effects of serum and lipoproteins on steroidogenesis in cultured bovine luteal cells. Molec. Cell. Endo. 28,551. Rayssiguier, Y., Mazur, A., Gueux, E., Reid, I. M., Roberts, C. J. (1988): Plasma lipoproteins and fatty liver in dairy cows. Res. Vet. Sci. 45,389. Reid, I. M. (1980): Incidence and severity of fatty liver in dairy cows. Vet. Rec. 107,281. Reid I.M. (1982-1983): Reproductive performance and fatty liver in Guernsey cows. Anim. Reprod. Sci. 5,275 Reid, I. M., Dew, S. M., Collins, R. A. (1983): The relationship between fatty liver and fertility in dairy cows: A farm investigation. J. Agric. Sci. Camb. 101,499. Scharrer, E., Langhans, W. (1988): Metabolic and hormonal factors controlling food intake. Internat. J. Vit. Nutr. Res. 58,249. Smith, J. A. (1987): Liver function parameters in highproducing postpartum dairy cows. Proceedings of the 5th Annual Veterinary Medical Forum, pp405. Targowski, S. P., Klucinski, W. (1983): Reduction in mitogenic response of bovine lympocytes by ketone bodies. Am. J. Vet. Res. 44,828. Targowski, S. P., Klucinski, W., Littledike, E. T. (1985): Suppression of mitogenic response of bovine lymphocytes during experimental ketosis in calves. Am. J. Vet. Res. 46,1378. van Dijk, S., Wensing, Th., Wentink, G. H., Jorna, T. J. (1989): Hepatic lipidosis in dairy cows related to health and fertility. Proceedings, 7th International Conference on Production Disease in Farm Animals, pp289. Williams, G. L. (1989): Modulation of luteal activity in postpartum beef cows through changes in dietary lipid. J. Anim. Sci. 67,785. York, D. A. (1990): Metabolic regulation of food intake. Nutr. Rev. 48,64. Zamet, C. N., Colenbrander, V. R., Callahan, C. J., Chew, B. F., Erb, R. E., Moeller, N. J. (1979): Variables associated with peripartum traits in dairy cows. I. Effect of dietary forages and disorders on voluntary intake of feed, body weight and milk yield, Theriogenology 11,229. Zamet, C. N., Colenbrander, V.F., Erb, R.E., Callahan, C.J., Chew, B.P., Moeller, N. J. (1979): Variables associated with peripartum traits in dairy cows. II. Interrelationships among disorders and their effects on intake of feed and reproductive efficiency. Theriogenology 11,245.

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